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THC & TROPACOCAINE

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DEDICATION

I dedicate this book to all those who suffer with post traumatic stress disorder, allergies, anorexia, migraines, insomnia and any other afflictions of the anandamide neurotransmitter system.

I want to thank the US, Great Britain, and German Patent Offices; DEA, USDA; PILOTS; NIDA; and the NIMH for their support of brain-mind research. I also want to thank the scientists, physicians, activists, lawmakers, attorneys, and law enforcement who dedicate their lives to helping those who are suffering.

TABLE OF CONTENTS

Chapter	Page
Reader’s Notice -----	viii
Preface -----	viv
THC	
1 Medical Cannabis -----	1
<i>CANNABIS. U.S. (Br.) CANNABIS Cannab</i> -----	2
THC -----	10
Synhexyl -----	11
2 Stereochemical Requirements	
for Cannabimimetic Activity -----	13
3 Cannabinoid Receptors -----	31
CB2 Agonist Treament of Autoimmunine Disorders -----	34
CB-2 Receptor Agonist Compounds -----	35
Inhibition of Cell Proliforation -----	36
Cannabinoids in the Treatment of Glaucoma -----	36
Anandamide Amidase Inhibitors as Analgesic Agents ---	37
CB1 Agonists for Use in Brain Trauma -----	38
Erratic Gastrointestinal Absorbtion	
of delta-9-Tetrahydrocannabinol -----	39
Treating Mental Diseases, Inflammation	
and Pain with Anandamides -----	40
4 Cannabinoid Extraction -----	41
Extraction of Delta-9-Tetrahydrocannabinol	
from <i>Cannabis</i> -----	42

Extraction of <i>Cannabis</i> Buds (41% THC Oil) -----	43
Extraction of Cannabis Buds 2 (40% THC Oil) -----	44
Direct Fractional Distillation of the Hexane Extract (92% THC Oil) -----	44
Preparing Delta-9-Tetrahydrocannabinol -----	45
Direct Treatment of Cannabis Extracts with Methanolic KOH Solution (70% THC Oil) -----	45
Reprocessing of the Residue Left After Fractional Distillation of Cannabis Extracts (82% THC Yellow Oil) -----	45
5 THC Syntheses -----	47
Water Soluble Derivatives of Cannabinoids -----	47
Synthesis of Compound (4) Ketones from Nitriles -----	47
NMDA-blocking pharmaceuticals -----	48
THC in the Treatment of Glaucoma in Patients who can not take Beta-blockers -----	50
Compositions useful as a cannabinoid receptor probe ---	51
NMDA-blocking Pharmaceutical Compositions -----	52
Production of 6,12-Dihydro-6-hydroxy-cannabidiol and the use Thereof for the Production of <i>trans</i> -delta-9-Tetrahydrocannabinol -----	53
Production of 6,12-Dihydro-6-hydroxy-cannabidiol -----	56
Production of <i>trans</i> -delta-9-Tetrahydrocannabinol -----	56
Preparation of <i>cis-p</i> -Menth-2-ene-1,8,-diol -----	57
Novel Tetrahydrocannabinol Type Compounds -----	57
Preparation of (-)-6a,10a- <i>trans</i> -6a,7,8,10a- Tetrahydrodibenzo[b,d]-pyrans -----	59
Preparation of Optically Active <i>trans</i> -Hexahydrodibenzopyranones -----	61
1-Hydroxy-3-(1,1-dimethylheptyl)-6,6-dimethyl- 6,6aR,7,8,10,10aR-hexahydro-9-H- dibenzo[b,d]pyran-9-one -----	63
Producing 6a,10a- <i>trans</i> -6a,7,8,10a- Tetrahydrodibenzo (b,d)-pyrans -----	64
Dibenzo[b,d]pyrans and Process -----	68
3-(1,2-Dimethylheptyl)-6a,7,10,10a-tetra-hydro- 1-hydroxy-6,6,9-trimethyl-6H-dibenzo [b,d]pyran -----	70
6 5-Alkylresorcinols -----	71
Preparation of 1-Hydroxy-2,6-dimethoxy- 4-(tertiary alkyl)benzene -----	71
1-Hydroxy-2,6-dimethoxy-4-(1,1-dimethylheptyl)benzene -----	72

Divarin Dimethyl Ether from	
3,4,5-Trimethoxy-propiofenone -----	73
Reduction of Ketones to Resorcinols -----	74
Synthesis of 5-Alkylresorcinols -----	74
Synthesis of 5-Ethylresorcinol -----	74
Preparation of Hexylresorcinol by	
Electrolytic Reduction of Hexanoylresorcinol -----	74
Synthesis of 5-Methylresorcinol (Orcinol) -----	75
5-Alkylresorcinol from Demethylation of	
1-(Alkyl)-3,5-Dimethoxybenzene -----	75
Demethylation Using Pyridine	
5-(1,1-dimethylheptyl)resorcinol -----	76
Demethylation Using 48% Hydrobromic Acid	
5-(1,1-Dimethylheptyl)resorcinol -----	76
Preparation of 5-Alkoxyresorcinols -----	77
Preparation of Phloroglucinol and its Mono-ethers -----	78
Preparation of Compounds with Marijuana Activity ----	81
Formation of Tetrahydrocannabinols by	
Isomerization of Cannabidiol -----	82
A. By <i>p</i> -toluenesulfonic acid -----	82
B. By sulfuric acid -----	83
C. By pyridine hydrochloride -----	83
D. By phosphoric acid -----	83
E. Sulfamic acid; zinc chloride -----	84
7 Isomerisation -----	81
Converting <i>cis</i> -Hexahydrodibenzo[b,d]pyran-9-ones	
to <i>trans</i> -Hexahydrodibenzo[b,d]-pyran-9-ones -----	85
<i>dl-trans</i> -1-Hydroxy-3-(1,1-dimethyl-heptyl)	
-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-	
dibenzo[b,d]pyran-9-one -----	86
<i>dl-trans</i> -1-Hydroxy-3-n-pentyl-6,6-	
dimethyl-6,6a,7,8,10,10a-hexahydro-	
9H-dibenzo[b,d]pyran-9-one -----	87
<i>dl-trans</i> -1-Hydroxy-3-(1,1-dimethyl	
heptyl)-6,6-dimethyl-6,6a,7,8,10,10a-	
hexahydro-9H-dibenzo[b,d]pyran-9-one -----	87
Stereoselective Preparation of Hexahydro	
dibenzopyranones and intermediates therefor -----	88
(-)- <i>trans</i> -1-Hydroxy-3-(1,1-dimethyl-heptyl)-6,6-	
dimethyl-6,6a,7,8,10,10a-hexahydro-	
9H-dibenzo[b,d]pyran-9-one -----	88
Acetylation of THC -----	89

8	Delta 1-THC-7-oic acid Analgesic and Anti-inflammatory Agents	91
	Platelet Activating Factor Antagonist	95
	Non-psychoactive Derivatives of Δ^6 -THC-7-oic Acid which have Analgesic and Anti-inflammatory Properties	97
	Synthesis of (3R,4R)- Δ^6 -THC-DMH-7-oic Acid Acetate	97
9	Andanamides: Fatty Acid Amides	99
	Preparation of Arachidonyl Ethanolamide	101
	Compounds Isolated from the Brain and Synthesized	103
	Synthetic Compounds Prepared and Tested	103
	Anandamide Amidase Inhibitors as Analgesic Agents	104
	Treating Anxiety and Mood Disorders with Oleamide	106
	Oleamide	108
10	Fatty Acid Amides Preparation from Common Household Oils	111
	Preparation of Oleamide	111
	The Reactions Used	111
	N-Substituted Amides of Natural Fatty Acids	112
	Preparation of	
	N-Methyl Linseed Oil Fatty Acid Amide	113
	Preparation of	
	N-Cyclohexyl Linseed Oil Fatty Acid Amide	113
	Preparation of Lauric Diethanolamide from Lauroyl Chloride	114
	Preparation of Cocoa Fatty Acid Amide Using the Aminolysis Method	115
	Industrial Manufacture of Fatty Acid Ethanolamides	115
	Preparation of Oleic Acid Monoethanolamide	116
	Purification of Fatty Acid Amides Using Urea	117
	Preparation of Olive Oil and Coconut Oil Ethanolamides	117
	Preparation of Fatty Acids	118
	Isolation of Linoleic Acid	118
	Isolation of Oleic Acid from Olive Oil	118
	Production of Monoalkylamines	118

TROPACOCAINE

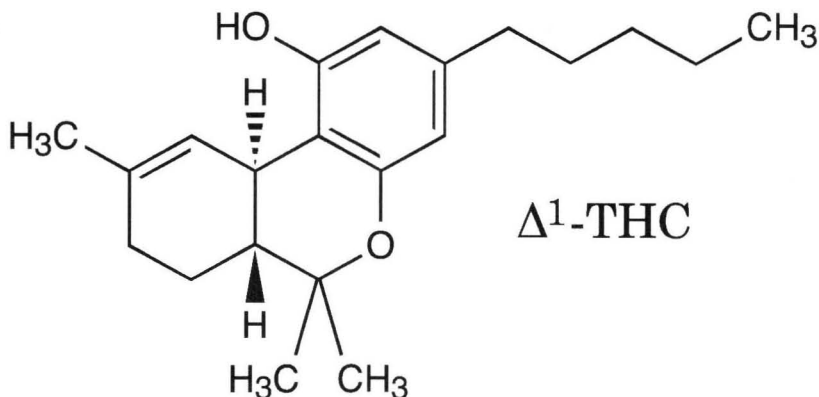
1	Coca, The Source of Cocaine -----	119
	Coca -----	122
2	Cocaine -----	127
	COCAINA. <i>U.S., Br.</i> -----	131
	COCAINE HYDROCHLORIDUM. <i>U.S., Br.</i> -----	134
3	Atropine and the Tropeines -----	141
	Cocaine and the Local Anesthetics -----	143
4	Tropacocaine -----	147
	Tropacocaine -----	148
	Benzoyl Ester of Ecgonine Using Benzoic Anhydride ----	149
	Tropacocaine from Pseudo-tropine & Benzoic Anhydride	149
	Pseudotropine by Electrolytic Reduction of Tropine ----	151
	Tropineone by Oxidation of Tropine -----	151
	Extraction of Pseudotropine -----	152
	Pseudotropine	
	by the Electrolytic Reduction of Tropinone -----	152
	Tropinone by the Oxydation of Tropine -----	152
	Tropinone by the Oxydation of Pseudotropine -----	152
	Tropinone by the Electrolytic Reduction	
	of Tropine or Pseudotropine -----	153
	Benzoic Anhydride -----	153
5	Narcotic Daturas -----	157
	Origin of the Name Jimson, or Jamestown Weed -----	159
	The Huaca-Cachu of Peru -----	161
6	Datura Alkaloids -----	165
	Hyoscyamine and Atropine -----	165
	Atropine Sulphate -----	166
	Hyoscine or Scopolamine -----	167
	Extraction of Atropine -----	167
7	Growing Datura and Related Species -----	169
	BELLADONNA <i>Atropa belladonna</i> -----	169
	<i>Atropa belladonna</i> (Belladonna) Cultivation -----	171
	<i>Datura stramonium</i> L. (Jimson Weed) -----	173
	<i>Datura stramonium</i> (Jimson weed) Cultivation -----	174
	<i>Hyoscyamus niger</i> (Henbane) Cultivation -----	175
	<i>Solanum nigrum</i> L. (Black Nightshade) -----	176
	Suggested Reading -----	177
	Bibliography -----	177

READER'S NOTICE

This book is a tool for the legal, medical, scientific and political professions and should not be misconstrued as a 'cookbook'. Publisher and author take no responsibility for inaccuracies, omissions, or typographical errors. References and sources are included for those seeking unedited detailed descriptions on the construction of any specific molecule. All chemicals and reactions are potentially toxic, explosive & lethal. Check NTP and OSHA databases for toxicology data.

This book is for information purposes only. No person is allowed to produce controlled substances without proper permits and authorization. To take/give substances for human consumption whether legal or illegal without a very thorough knowledge of the substance and the health (mental as well as physical) condition/s of the individual is destined to produce catastrophic results and legal ramifications.

This guide is an asset and a necessity for:
physicians, lawmakers, teachers, counselors,
attorneys, law enforcement and students alike.



Preface

THC is a new miracle medication. It is being used in the form of marijuana throughout the world for medical uses. During the 1990's many states began decriminalizing the plant for personal cultivation by patients. Patients that use cannabis medicinally are not criminals.

Marijuana was illegalized in 1937; the law being a guise for the deportation of Mexicans following WWI. Mexican migrant workers smoked cannabis, so the law. Mexican migrant workers are an assent and integral part in the agriculture industry, they should be treated fairly and with respect.

Anslinger, who pushed the illegalization to Congress, at first, did not want medical marijuana illegalized. Nor did he feel that it was a problem in other states. He was being pushed by California, Arizona, Colorado and Texas to get federal help to get rid of the Mexicans. Anslinger's claims to Congress were pure propaganda. The Laguardia Report contradicted Anslinger's bull slinging to no avail. Only in the past few decades have officials begun to understand that marijuana is much safer than originally claimed in depression era propaganda and bigotry. Using marijuana (CB1 agonist), post-trauma, protects neurons.

THC works by blocking an enzyme that breaks down anandamide. The anandamide family of neurotransmitters control sleep, inflammation, memory etc. In PTSD patients, multi-symptoms can be temporarily shut down with cortisone. They are super-suppressors when challenged with the dexamethasone suppression test (Yehuda 1993; 2002). Unfortunately, many patients can not tolerate and are very sensitive to cortisone (glucocorticoid drugs) (Sapolsky 2002) and other drugs such as SSRIs (Marshall 2002). THC partially binds to endogenous glucocorticoid receptors and down regulates them (Eldridge 1990). PTSD patients experience a profound reduction in sleep disorders, obsessive compulsive thoughts, and flashbacks (Marsicano 2002).

Victims of torture/terrorism with PTSD can react violently (Hoppe 1971; Feldman 1988), the use of marijuana reduces this aggression (Myerscough 1985; Ree 1984). THC is the only drug available which is safe and effective to treat some of the multi-afflictions of PTSD patients. Marinol has been noted to produce short term benefits. The dronabinol (THC) is mixed with sesame oil which has a laxative action. Laxatives can produce GI disease. Patients have found marijuana to be a more tolerable and effective medication with no GI side effects.

Anandamides can be produced with little investment (eg argon tank, a fatty acid) and yield unlimited quantities. Many of these fatty acid amides are CB1 agonists and will replace both THC and cannabis.

“The estimated lifetime prevalence of PTSD among adult Americans is 7.8%, with women (10.4%) twice as likely as men (5%) to have PTSD at some point in their lives.” Source: PILOTS Database

When walking in large gatherings, I always felt safer when I smell cannabis in the air. Law enforcement, at several large events, have mentioned to me that they did not confiscate cannabis from people. An officer was standing watching the crowd as people were passing joints. “We’ve had fights and riots at large gatherings in the past. Cannabis chills people out. I’m a peace keeper, not a politician,” he remarked.

I will not advocate that anyone buy marijuana as it could be unsafe from the street. Buyers clubs offer patients quality control. States that run their own liquor stores could replace buyers clubs. Cannabis could be regulated by the government, fatty acids amides such as anandamide type molecules (CB1 agonists) can not be controlled as they can be made from grocery store oils.

Millions of Americans are addicted to cocaine, yet there has been no development in safe or effective alternatives. Many of the new medications increase dopamine in the brain, and should be tried by anyone who has a cocaine habit. Those that are highly addicted, tropacocaine might be a lesser toxin (eg. methadone instead of heroin). At this time there are no studies on tropacocaine being conducted in the US.

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Illegal Drugs and How They Got That Way; Marijuana; History Channel.

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Myerscough, R.; Taylor, S.; The Effects of Marijuana on Human Physical Aggression; *Journal of Personality and Social Psychology* (1985) 49 (6) 1541-1546

Ree, J.M.; Niesink, J.M.; Nir, I.; Δ 1-Tetrahydrocannabinol but not Cannabinol Reduces Contact and Aggressive Behavior of Rats Tested in Dyadic Encounters; *Psychopharmacology* (1984) 84: 561-565

Sapolsky, R.; Glucocorticoids and Hippocampal Atrophy in neuropsychiatric Disorders; *Archives of General Psychiatry* (2002) 57(10): pp. 925-935

Yehuda, R.; Enhanced Suppression of Cortisol Following Dexamethasone Administration in Posttraumatic Stress Disorder; *American J. Psychiatry* (1993) 150: 83-86

Yehuda, R.; Neuroendocrine Alterations in Posttraumatic Stress Disorder; *Primary Psychiatry* (2002) 9(2): pp. 30-34

Chapter 1: Medical *Cannabis*

by Walter Ernest Dixon MD., B.S., B.Sc. Lond.,
D.P.H. Camb. November 11, 1899

“On man the effect of the inhalation of the fumes from powdered ganja (the dried flowering tops coated with resin) produces an exhilaration and refreshed feeling which is particularly noticeable after fatigue, mental or physical; the effects are more pronounced than those produced by either tea or alcohol, and give rise to no noticeable subsequent reaction. Further, the feelings of the patient are sufficient to regulate the dose, and there is little danger of taking an excess. Should the inhalation be continued after the desired effect has been produced he loses some self-control, manifests a desire to laugh at everything, and becomes very talkative. In the space of some twenty minutes to half an hour the normal condition recurs, and all the feelings of exhaustion, headache, etc., have disappeared.

Effects on: Gastrointestinal. - No effect has been noticed tending either towards constipation or diarrhea. After moderate inhalation the general stimulating effect extends to the stomach, and an increased appetite is noticeable, so much so that it may even be regarded as a useful food accessory.

By the mouth one hour to two hours are necessary before absorption occurs, the effects produced being more lasting than when it is inhaled. Taken as an inhalation may be placed in the same category as coffee, tea, and kola. It is not dangerous and its effects are never alarming, and I have come to regard it in this form as a useful and refreshing stimulant and food accessory, and one whose use does not lead to habit which grows upon its votary.

Finally, from a frequent observation, both subjective and objective, I can affirm that it is soothing and stimulating, being when inhaled a specially valuable cerebral stimulant. I believe it to be an exceedingly useful therapeutic agent, one not likely to lead to abuse, and producing in proper dosage no untoward after-effects.”

Source: Dixon 1899

CANNABIS. U.S. (Br.) CANNABIS Cannab.

by Horatio C. Wood, Jr., M.D.

1926

"*Cannabis* is the dried flowering tops of the pistillate plants of *Cannabis sativa* Linné (Fam. *Moraceae*). *Cannabis*, in the form of the fluidextract, administered by the mouth to dogs in doses not exceeding 0.1 cc. for each kilogram of body weight of dog, produces a degree of incoordination equivalent to that caused by the same dose of the standard fluidextract of *cannabis*, prepared as directed below. It contains not more than 10 per cent. of its fruits, large foliage leaves, stems over 3 mm. in diameter, and not more than 2 per cent. of other foreign organic matter. It yields not more than 5 per cent. of acid-insoluble ash, and not less than 8 per cent. of alcohol-soluble extractive." *U.S.*

"Indian Hemp consists of the dried flowering or fruiting tops of the pistillate plant of *Cannabis sativa*, Linn., grown in India; from which the resin has not been removed." *Br.*

Cannabis Indicae, *Br.*, Hemp, Indian Hemp, Gunza Ganjah, Herba *Cannabis Indicae*; Chanvre, Chanvre de l'Inde, *Fr.*; Indischer Hanf, *G.*; Cañamo, *Sp.*; Marihuana, *Mez.*

For many years the official cannabis was restricted to the drug which was used for centuries in India. The reason for this was that the Indian *cannabis* was more uniformly active. Recently the Indian Government has placed a high tax on every pound of the drug grown. The result has been that other markets have been sought and the hemp plant has been grown in other parts of Asia, Africa and America. While, of course, much of this material is not equal to that grown in India yet the fact that it can be grown, as shown by experiments, in the United States (see Hamilton, *J. A. Ph. A.*, 1913, ii; 1915, iv, 389) of a very high quality has caused the framers of the *U.S. Pharmacopeia* to permit the use of a cannabis, no matter where it may be grown, provided it comes up to the biological standard as given in the definition. Physiologically active cannabis is obtained at the present time not only from India, but Africa, Turkey, Turkestan, Asia Minor, Italy, Spain and the United States.

The *Cannabis sativa*, or hemp plant, is a tall, rough annual, from four to sixteen feet or more in height, with erect, branching, angular stem. The leaves are alternate or opposite, and palmately-compound, with five to seven linear-lanceolate, coarsely serrated leaflets. The stipules are subulate. The flowers are axillary and greenish; the staminate in long, branched, drooping panicles; the pistillate in erect,

simple catkins. The stamens are five, with long pendulous anthers; the pistils two, with long, filiform, glandular stigmas. The fruit is an ovate achene. The whole plant is covered with a fine pubescence, scarcely visible to the naked eye, and somewhat viscid to the touch. The hemp plant of India has been considered by some as a distinct species, and named *Cannabis indica*; but the most observant botanists, upon comparing it with our cultivated plant, have been unable to discover any specific difference. It is now, therefore, regarded merely as a variety. Pereira states that in the female plant the flowers are somewhat more crowded than in the common hemp, but that the male plants in the two varieties are in all respects the same.

C. sativa is a native of the Caucasus, Persia, and the hilly regions in Northern India. It is cultivated in many parts of Europe and Asia, and largely in our Western States.

The most important commercial varieties of *cannabis* are the India, American and African. Indian *cannabis* is obtained from plants grown in various districts of India, chiefly north of Calcutta. The flowering tops are collected when they have taken on a brownish color, the fruits shaken out and the herbage allowed to wilt and then subjected to the rolling and treading process in order to work resinous matter from the stems into the inflorescences. There are two commercial grades of Indian cannabis, viz.: round and flat. The round is prepared by kneading each branch into a cylindrical or rounded mass. The flat grade is kneaded into a compressed flattened form. The color is grayish-brown. The commercial supplies of this variety are imported into the United States from Bombay, India.

American *cannabis* is yielded by *Cannabis sativa* plants cultivated in various sections of the United States. It occurs on the market in the form of broken segments of the inflorescences and more or less crumpled and broken leaves, varying in color from brownish-green to light brown.

African *cannabis* from *Cannabis sativa* plants growing in various districts of Africa, comes into the market as broken leaves and flowering tops of a greenish-brown color.

The fruits or "so-called" seeds, though not now official, have been used in medicine. They are from three to five millimeters long and about two millimeters broad, roundish-ovate, somewhat compressed, of a shining ash-gray color, and of a disagreeable, oily, sweetish taste. For a comprehensive monograph on the morphology of *cannabis* fruits, as well as their history and chemical composition, see Tschirch, "*Handbuch der Pharmakognosie*," p. 555. They yield by expression about 20 per cent. of

a fixed oil, which has the drying property, and is used in the arts. They contain also uncrystallizable sugar and albumen, and when rubbed with water form an emulsion, which may be used advantageously in inflammations of the mucous membrane, though without narcotic properties. The seeds are much used as food for birds, as they are fond of them. They are generally believed to be in no degree poisonous; but Michaud relates the case of a child in whom serious symptoms of narcotic poisoning occurred after taking a quantity of them. It is probable that some of the fruit eaten by the child was unripe, as in this state it would be more likely to partake of the peculiar qualities of the plant.

In Hindostan, Persia, and other parts of the East, hemp has long been habitually employed as an intoxicating agent. The parts are the tops of the plant, and resinous product obtained from it. *Bhang* is the selected, dried and powdered leaves. *Ganjah* or *gunjah* is the tops of cultivated female plants, cut directly after flowering, and formed into round or flat bundles from two to four feet long by three inches in diameter. It is stated that in the province of Bengal great care is taken to eradicate the male plants from the fields before fertilization of the female, and that thereby the yield and quality of the resin is greatly increased. In Bombay this matter is commonly neglected, so that Bengal *ganjah* is much superior to Bombay *ganjah*. It is recognized in India that *ganjah* rapidly deteriorates on keeping, that which is one year old being not more than one-quarter as potent as the fresh drug, while two-year-old *ganjah* is practically inert and is required by the Indian government to be burned in the presence of excise officers. It is probable) however, that much old *ganjah* finds its way into the markets of the world.

The method of collection in Baluchistan is to gently rub the dried plant between carpets. The dust which comes off contains the active principle and is known as "*rup*." The second shaking produces an inferior variety, known as "*tahgalim*," and the third shaking is known as "*ganja*." In Nepal the plant is squeezed between the palms of the hands, and the resin scraped off from the hands. These balls, and also masses formed out of resin mechanically separated from the hemp plant are called charas or churrus. This is the hashish or hasheesh of the Arabs.

Hashish is also produced in considerable quantities in Persia by rolling and rubbing the flowers, stalks and leaves of hemp on rough woollen carpets and subsequently scraping off with a knife and making into balls or sticks the adherent resinous substance. The carpets are afterwards washed with water and the extract obtained by evaporation sold at a low price.

Momea or *mimea* is a hemp preparation said to be made in Thibet with human fat.

The pistillate plants are much more active than the staminate and when hemp is grown for its drug it is the custom to eradicate the latter, pruning the remaining female plants so as to make them branch more luxuriantly.

Properties.—Fresh hemp has a characteristic odor, which is much less in the dried tops, which have a feeble bitterish taste.

Description and Physical Properties.—

“Unground *Cannabis*.—In separate tops or less agglutinated masses or fragments, consisting of the short stems with their leaf-like bracts and pistillate flowers or more or less developed fruits; color green to dark green or greenish brown; odor agreeable, somewhat heavy and narcotic; taste somewhat acrid and pungent. Leaves digitately compound, usually broken. Leaflets when entire, linear-lanceolate, nearly sessile, margin deeply serrate. Bracts ovate, pubescent, each enclosing 1 or 2 pistillate flowers or more or less developed fruits. Calyx dark green, pubescent and somewhat folded around the ovary. Styles 2, filiform and pubescent. Ovary with a single campylotropous ovule. Stems cylindrical, longitudinally furrowed, light green to light brown, strigosepubescent.

“Structure of Stem.—Cortex composed of collenchyma and, in the larger stems, of numerous strands of more or less lignified bastfibers; strongly lignified wood with medullary rays 1-cell wide; pith, often hollow; rosette aggregates of calcium oxalate numerous.

“Powdered *Cannabis*.—Dark green; epidermis from lower surface of leaves with sinuate vertical walls and numerous oval stomata, from upper surface with straight walls and no stomata; non-glandular hairs numerous, unicellular, rigid, curved, with a very slender pointed apex and an enlarged base usually containing calcium carbonate masses; glandular hairs of two kinds, one with a short 1-celled stalk, the other with a long multicellular, tongue-shaped stalk, the head being globular and consisting of 8 to 16 cells; fragments of bracts and leaves showing yellowish-brown laticiferous vessels, numerous rosette aggregates of calcium oxalate, 0.005 to 0.030 mm. in diameter, and strands of spiral tracheae and phloem; fragments of fruits with palisade-like, non-lignified cells with yellowish-brown finely porous walls usually containing air; tissues of embryo and endosperm with numerous oil globules and aleurone grains, the latter from 0.005 to 0.010 mm. in diameter and displaying crystalloids and globoids. Diluted hydrochloric acid added to powdered *Cannabis* causes effervescence visible under the microscope.” U.S.

The *British Pharmacopoeia* describes Indian *cannabis* as follows:

"In compressed, rough, dusky-green masses, consisting of the branched upper part of the stem, bearing leaves and pistillate flowers or fruits, matted together by a resinous secretion. Upper leaves simple, alternate, 1-3 partite; lower leaves opposite and digitate, consisting of five to seven linear-lanceolate leaflets with distantly serrate margins. Fruit one-seeded and supported by an ovate-lanceolate bract. Both leaves and bracts bear external oleo-resin glands and one-celled curved hairs, the bases of which are enlarged and contain crystalloids. Strong, characteristic odor; taste slight. When a mixture of 10 grammes of finely powdered Indian Hemp and 100 millilitres of alcohol (90 per cent.) is shaken occasionally during twenty-four hours and then filtered, 20 millilitres of the filtrate, evaporated in a flat-bottomed dish, yield a residue weighing, when dried at 100° C., not less than 0.250 gramme. Ash not more than 15 per cent." *Br.*

For a histological description of the leaf by A. R. L. Dohme, see *Proc. A. Ph. A.*, 1897, 569. The *cannabis* of the market may consist of fruiting tops and stems and occasionally the staminate tops are admixed with it.

William Beam in Bulletin No. 4 of the chemical Section of the Wellcome Tropical Research Laboratories, Khartoum, has discovered a specific color reaction which may be used for the detection of *Cannabis indica* and its preparations. A petroleum ether extract of the suspected material is prepared and evaporated to dryness in a test tube. To this is added a few cc. of a reagent prepared by saturating absolute alcohol with dry hydrogen chloride gas. In the presence of *cannabis* the liquid assumes a bright cherry red color which is destroyed upon the addition of water or alcohol.

Constituents.—The activity of hemp undoubtedly resides in its resin, but the chemical nature of the active principle is unsettled. By repeated distillation of the same portion of water from relatively large quantities of hemp renewed at each distillation, M. J. Personne obtained a volatile oil, of a stupefying odor, and an action on the system such as to dispose him to think that it was the active principle of the plant. This oil was lighter than water, of a deep amber color, a strong odor of hemp, and composed of two distinct oils, one colorless, with the formula $C_{18}H_{20}$, the other a hydride of the first, $C_{18}H_{22}$, which was solid, and separated from alcohol in plate-like crystals. For the former Personne proposes the name of cannabene. It is affirmed that when this is inhaled, or taken into the stomach, a singular excitement is felt throughout the system. followed by a depression, sometimes amounting to syncope, with hallucinations which are generally disagreeable, but an action on the

whole slighter and more fugitive than that of the resin. Cannabindon, $C_8H_{12}O$, is a dark red syrupy liquid obtained by Kobert (*Chem. Ztg.*, 1894, 741) from *Cannabis indica*; it is soluble in alcohol, ether and oils; it is affirmed to be narcotic in doses of from half a grain to two grains (0.032-0.13 Gm.). As a result of a reinvestigation of *charras* (*churrus*) from Indian hemp, Wood, Spivey, and Easterfield (*J. Chem. S.*, vol. lxi, 539) have found the following principles: 1, a terpene, boiling between 150° and 180° C.; 2, a sesquiterpene, boiling at 258° to 259° C.; 3, a crystalline paraffin of probable formula $C_{29}H_{60}$, melting at 63.5° C.; and 4, a red oil, boiling at 26.5° to 270° C. under a pressure of 20 mm., to which they give the name cannabinol, and the formula $C_{18}H_{24}O_2$. This latter constituent they consider the only active ingredient. It is probably the same substance as the dark red syrup of Kobert, mentioned above under the name of cannabindon. The authors found that cannabinol readily underwent superficial oxidation, at the same time losing its toxic activity. It is stated that cannabinol exhibits much more powerful effects when dissolved in a bland oil such as olive oil. Fränkel (*A.E.P.P.*, 1903, p. 266) claims to have isolated the active principle of hashish as a pure and chemically well defined body. It has the formula $C_{21}H_{30}O_2$, and is a phenol-aldehyde. It is of a pale yellow color and of a thick consistency. When heated it becomes quite fluid and distills at 215° C., under a pressure of 0.5 mm. It oxidizes in the air, acquiring a brown tint. It responds to Millon's reaction, and can be acetylated, showing thus its phenol character. Fränkel proposes that the name cannabinol be given to it and that the term pseudo-cannabinol be given to the substance of Wood, Spivey and Easterfield which Frankel asserts is inert.

"Assay.—Hooper (*P.J.*, 1909, lxxxi, p. 80) describes a method for the chemical standardization of *cannabis* based upon its iodine value. He finds that the alcoholic extract of old samples has a lower iodine value than that from recent specimens, and there is more or less constancy of relation between the age and the iodine value.

The *U.S. Pharmacopoeia* gives a physiological test for the standardization of *Cannabis indica*. Up to the present no means have been suggested for determining, with even approximate accuracy, the relative potency of different samples of *Cannabis indica*, the physiological test simply demonstrating that the drug possesses a certain indefinite amount of physiological action. The official test is based on the degree of inco-ordination produce in the dog in comparison with that produced by a standard preparation. It is advisable to use the same animal for repeated tests, because the individual susceptibility of the dog varies so greatly, and the experimenter gradually learns the degree

of reaction to be expected from a certain dog. It is convenient to employ two dogs (fox terriers usually react well) to one of which will be given the standard and to the other the drug to be tested. Three days later the test should be repeated in reverse order, that is the dog which at the first test received the standard, at the second test should receive the unknown and vice versa. A fluidextract of the specimen to be tested is either evaporated into a soft extract and given in the form of a pill or mixed with an inert absorbing powder and enclosed in a capsule; it must not be given hypodermically. The symptoms caused by *Cannabis indica* in the dog recall those of alcoholism in the human being. There is at first a slight loss of control in the hind legs so that the animal staggers as he walks, later the ataxia becomes so marked that the dog is unable to stand up without leaning against some object, and about this time begins to show distinct drowsiness, and may eventually pass into a heavy sleep.

"Use adult dogs which weigh less than 15 kilogrammes and which are susceptible to the action of *Cannabis*. The dogs must not be fed for twelve hours before being used and observations should be made within one hour after administration. The same animal must not be used for testing purposes at shorter intervals than three days. Administer the fluidextract in gelatin capsules by the mouth." *U.S.*

Standard Fluidextract of *Cannabis*.—In order to obviate the inaccuracies due to variations in susceptibility of the dogs, the present *Pharmacopoeia* directs a comparison to be made with a standard fluidextract of *cannabis*. This is directed to be prepared as follows:

"Prepare a composite fluidextract, representing at least ten different lots of *Cannabis*, conforming to the official botanical description, and administer this fluidextract in gelatin capsules to dogs by the mouth. This standard fluidextract must be so adjusted that it will produce incoordination in dogs which have been found to be susceptible to the action of *Cannabis* when administered in doses of 0.03 cc. for each kilogramme of body weight of dog." *U.S.*

The Bureau of Chemistry, U. S. Department of Agriculture, has indicated its willingness to supply such a standard fluidextract of *cannabis* for the use of those who desire to make biological assays of this drug.

It has generally been believed that *cannabis* deteriorates rapidly, but Eckler and Miller (*J.A. Ph.A.*, 1917, vi, p. 872) found that the crude drug showed practically no change after a year's storage but that after two years it had lost about half of its potency; Hamilton (*J.A.Ph.A.*, 1918, vii, p. 117) believes that the loss must be usually much slower because he found a sample fourteen years old to be 70 per cent. of

standard, and an extract, which had been constantly used for assay purposes for nine years, has shown no appreciable change.

Uses.—Aside from a slight local irritant effect the action of cannabis seems to be limited almost exclusively to the higher nerve centers. In man this is first manifested by a peculiar delirium which is accompanied with exaltation of the imaginative function and later by a remarkable loss of the sense of time. The delirium is often accompanied with motor weakness and diminished reflexes and generally followed by drowsiness. In the dog the earliest manifestation of the drug's action is a slight degree of restlessness which is soon followed by disturbances of equilibrium and later weakness of the legs and drowsiness.

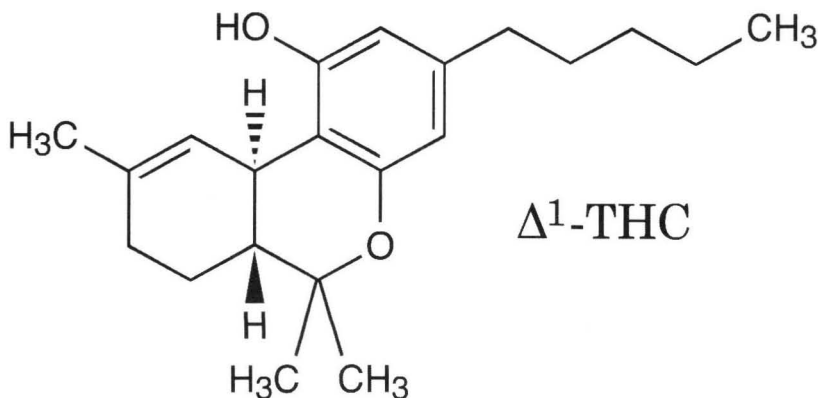
Cannabis is used in medicine to relieve pain, to encourage sleep, and to soothe restlessness. Its action upon the nerve centers resembles opium, although much less certain, but it does not have the deleterious effect on the secretions. As a somnifacient it is rarely sufficient by itself, but may at times aid the hypnotic effect of other drugs. For its analgesic action it is used especially in pains of neuralgic origin, such as migraine, but is occasionally of service in other types. As a general nerve sedative it is useful in hysteria, mental depression, neurasthenia, and the like. It has also been used in a number of other conditions, such as tetanus and uterine hemorrhage, but with less evidence of benefit. One of the great hindrances to the wider use of this drug is its extreme variability. We are inclined to the opinion that one of the important reasons for the lack of confidence in this drug has been insufficiency in dosage. Because of the great variability in the potency of different samples of *cannabis* it is well nigh impossible to approximate the proper dose of any individual sample except by clinical trial. Because of occasional unpleasant symptoms from unusually potent preparations, physicians have generally been overcautious in the quantities administered. While the inclusion of a physiological assay in the *Pharmacopoeia* has somewhat improved the quality of drug upon the market it must be remembered that the present method of standardization is not quantitatively accurate; all that can be hoped from this assay is the exclusion of inert samples. The only way of determining the dose of an individual preparation is to give it in ascending quantities until some effect is produced. The fluidextract is perhaps as useful a preparation as any; one may start with two or three minims of this three times a day, increasing one minim every dose until some effect is produced. According to C.R. Marshall (*L.L.*, 1897, i, also *J.A.M.A.* Oct., 1898) the deterioration of *cannabis* is due to the oxidation of cannabinal, which he has found to act upon dogs and cats as the crude drug.

Dose, of *cannabis*, one to three grains (0.065-0.2 Gm.).

Off. Prep.—*Extractum Cannabis, U.S. (Br.)*; *Fluidextractum Cannabis, U.S.*; *Tinctura Cannabis* (from Extract), *Br.*; *Collodium Salicylici Composita* (from Fluidextract), *N. F.*; *Mistura Chlorali et Potassii Bromidi Composita* (from Extract), *N. F.*; *Mistura Chloroformi et Morphinae Composita* (from Tincture), *N. F.* Source: Wood 1926

THC

by Roger Adams



“(45mg THC)... The result was a ravenous hunger which was not satisfied after eating the equivalent of two hearty meals... In spite of the intoxication with the resulting phenomena, this subject (industrial chemist) had no difficulty in holding his own and then some in a poker game composed of expert players.”

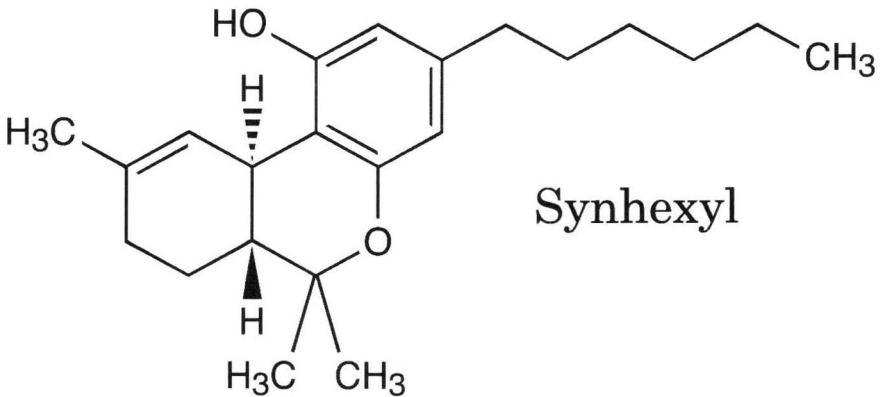
“Took two capsules... At 8:30 (PM) I devoured an enormous steak dinner with great rapidity and thoroughness, and left no trace of any of the fixings... I can’t write too enthusiastic an endorsement for this drug you fellows are synthesizing... The feeling of well-being would not, in my estimation, equal that from about three highballs,” college professor.

Source: Adams 1941-1942

Synhexyl

by G. Tayleur Stockings, M.B., B.S., D.P.M.

June 28, 1947



"Synhexyl is rather more potent weight for weight than natural cannabis, the effective dosage being from 5-15 mg. in normal subjects to 60-90 mg. in depressive patients. In narcotic drug addicts doses of 60-240 mg. three times daily may be given without ill effects (Himmelsbach).

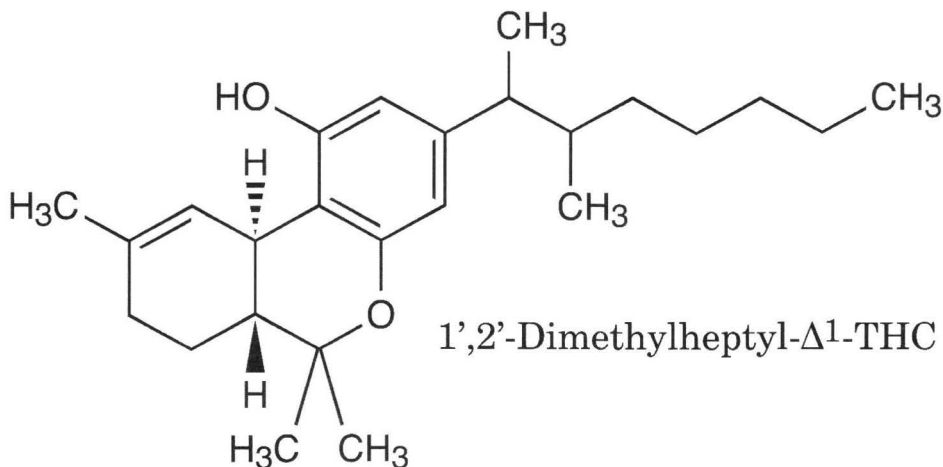
The general effects in normal man are as follows: there is first a latent period of 1-1/2 to 3 hours before any effect is felt, this being about twice the latent period for the same dose of *cannabis* extract. The onset of the synhexyl effect is characteristically abrupt, with a sudden and peculiar sensation of lightness and mild intoxication accompanied by acceleration of the pulse and feeling of slight palpitation and oppression in the head and chest. Transient feelings of anxiety and vertigo may occur at the onset, but this usually pass off in the course of a few minutes to half an hour. The euphoric effect quickly follows, and consists of a pleasant feeling of happiness and exhilaration with a marked sense of physical well-being and self-confidence; there is a sense of relief from tension and anxiety, and the threshold for unpleasant affect is markedly raised, while that for pleasant feeling-tone is correspondingly lowered. There is increased enjoyment of normally pleasant impressions, and zest for life and working capacity may be actually increased in the early stages of the intoxication. Later this effect gives way to a sense of dreamy apathy and contentment, which with larger dosages may reach the state of ecstasy. There is often increase speed of the stream of thought, with a marked increase in the power of fantasy and

vividness of visual imagery. With the larger dosages there may in the early stages be a tendency to flight of ideas and pressure of activity. In the sensory sphere there is little or no true analgesic effect of the opiate type. With the higher doses there may be some degree of blunting of sensation, but the senses of taste and hearing may actually become more acute. A generalized sensation of pleasant warmth diffused throughout the body is characteristic.

The average duration of the effects is from 8 to 10 hours from the time of onset of the symptoms.

Studies which I made on myself and a group of normal subjects show that with ordinary therapeutic doses there is little or no deleterious effect on the intellectual performance.

The results of these preliminary trials would suggest that we have in this class of compounds a promising therapeutic agent for the treatment of the chronic and intractable depressive states. Synhexyl, the most active of this class, has the advantages of low toxicity, minimum of side-effects, ease of administration, and chemical stability. Its use is not contraindicated by the presence of coexisting organic disease, and it is suitable for out-patient practice. Its use does not interfere with other therapeutic measures, such as occupational therapy and psychotherapy. It is free from the risks and disadvantages of the more drastic forms of treatment, and might replace those methods for the milder depression of later life where for any reason the more drastic procedures are contraindicated." Source: Stockings 1947

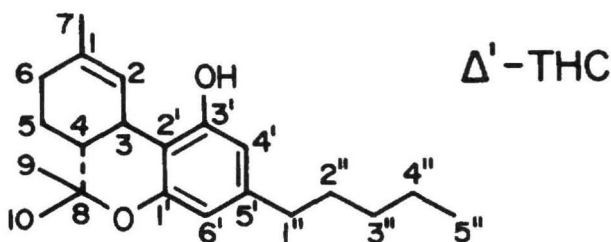


Chapter 2: Stereochemical Requirements for Cannabimimetic Activity

by Raphael Mechoulam, Ph.D.; Naphtali Lander, Ph.D.; Morris Srebnik, Ph.D.; Aviva Breuer, Ph.D.; Mark Segal, Ph.D.; Jeffery J. Feigenbaum, M.Sc.; Tobjorn U. C. Jarbe, Ph.D.; and Paul Consroe, Ph.D.

About 15 years ago, we formulated some tentative rules for cannabimimetic structure-activity relationships (SAR) (Edery et al. 1971; Mechoulam and Edery 1973). These rules were based on work our group had done since 1964, when we isolated and elucidated the structure of delta-1-tetrahydrocannabinol (delta-1-THC) (Gaoni and Mechoulam 1964), as well as on research by numerous other groups. Most of our work was done with rhesus monkeys; much of the work by the other groups was done with either rodents or dogs. However, gratifyingly, the results obtained with different species were qualitatively comparable.

Most of the rules have withstood the erosion of time, although exceptions have been noted and certain refinements have to be made.



The generalisations listed below apply today:

1. A dihydro-benzopyran type structure with a hydroxyl group at the 3' aromatic position and an alkyl group on the 5' aromatic position seems to be a requirement. Opening of the pyran ring generally leads to complete loss of activity. However, several major exceptions have been found, such as compounds (1) and (2) and some of their derivatives (Johnson and Melvin 1986). Hopefully, future work will throw light on these discrepancies.

2. The aromatic hydroxyl group has to be free or esterified. Blocking of the hydroxyl group as an ether inactivates the molecule. It is possible that the esters are actually inactive but undergo hydrolysis in vivo to the free phenols. Thus, delta-1-THC acetate, when tested in vitro, shows negligible activity in biochemical reactions in which delta-1-THC is active (Banerjee et al. 1975).

3. An all carbon side chain on C-5' is not an absolute requirement. The side chain may contain an etheric oxygen (e.g., compound 3) (Loev et al. 1973).

4. 7-Hydroxy THC's, which are major metabolites, are very potent cannabimimetics. Monohydroxylation on other position of the terpene ring also usually leads to active derivatives. Dihydroxylation generally causes loss of activity. Further oxidation of the C-7 hydroxyl group to a carboxyl group causes inactivation.

5. Hydroxylation on the C-1" of the side chain abolishes activity. Hydroxylation at the other side chain carbons retains activity with hydroxylation on C-3" potentiating activity. Some of these hydroxylated compounds have been detected as major metabolites.

6. Alkylation on the C-4' aromatic position retains activity; alkylation on the C-6' position eliminates activity. Electronegative groups, such as carbonyl or carboxyl, at either C-4' or C-6' eliminate activity.

7. The double bond isomers of THC show the following order of activity in humans: delta-1-THC > delta-6-THC > delta-3-THC (Hollister 1974). Delta-5-THC and delta-7-THC are inactive in animal tests, while delta-2-THC and delta-4-THC have not been tested yet.

8. The 7-methyl group is not an absolute requirement for activity: 7-nor-delta-1-THC (4) and 7-nor-delta-6-THC (5) are active in dogs (Wilson and May 1974).

9. The terpenoid ring may be exchanged by some heterocyclic systems (Pars et al. 1977; Lee et al. 1983).

10. The 1,1- or 1,2-dimethyl heptyl (DMH) side chain strongly potentiates the cannabimimetic activity of compounds which have low activity in the n-pentyl series.

The above rules are, in reality, approximations. In the cannabinoid series, for example, compounds which are considered inactive in some tests frequently show low activity in other cannabimimetic tests.

The above SAR findings do not cover stereochemical requirements for cannabimimetic activity. In the present summary, we will bring up to date the SAR in this area, with emphasis on as yet unpublished material from our laboratories.

C-1 EPIMERS

Reduction of the double bond in delta-1- or delta-6-THC leads to the formation of two C-1 epimers (Gaoni and Mechoulam 1966). The equatorial epimer, in which the methyl group on C-1 is almost in the plane of the hexahydrocannabinol molecule (compound 6a), is about as active in the rhesus monkey as delta-6-THC and is about 20 times more active than the axial epimer (7a), in which the methyl group is below the plane (Mechoulam et al. 1980).

The same relationship is observed when the C-1 substituent is an acetoxymethyl group: epimer (6b), in which the C-1 substituent is equatorial, is active in monkeys at doses of 0.5 mg/kg while the axial epimer (7b) is inactive at doses 10 times higher (Mechoulam et al. 1980).

The same trend is observed in drug discrimination tests. Rats and pigeons trained to discriminate between the presence and absence of the effects of delta-1-THC (3 and 0.56 mg/kg, respectively) were tested for generalization with the two epimeric 7-hydroxy-hexa-hydrocannabinols (6c and 7c). Both epimers generalized with delta-1-THC in rats as well as in pigeons (table 1) (Jarbe et al. 1986). As expected, the equatorial isomer (6c) was considerably more active than the axial one (7c). Surprisingly, compound (6c) was only 5 to 7 times more active in the rat than (7c), while in the pigeon, compound (6c) was 85 times more active. Apparently, species specificity in this test is very pronounced.

TABLE 1

Discrimination of 7-OH-Hexahydrocannabinols
(6c and 7c) to delta-1-THC

Hrs	Δ 1-THC	Compound (6c) (equat)	Compound (7c) (axial)
Rats (i.p.)			
0.5	0.85 (0.94)	0.24 (0.95)	1.58 (0.98)
1.5	1.07 (0.94)	0.44 (0.997)	2.16 (0.96)
4.5	4.78 (0.79)	--	--
Pigeons (i.m.)			
0.5	0.53 (0.92)	0.03 (0.99)	2.60 (0.58)
1.5	0.16 (0.91)	0.02 (0.87)	1.72 (0.97)
4.5	0.25 (0.94)		
9.0	1.21 (0.70)		

Median dose (mg/kg) effect estimates, ED₅₀, according to logarithmic regression analysis and within brackets corresponding fits (r) for the regressions are given. Absence of an estimate (-) means no value in the dose-generalization curve determination was above 50% drug appropriate responding (% RDP). (Jarbe et al. 1986)

The above experimental data point out that, in the absence of other molecular changes, the planarity at the C-1 position determines cannabimimetic activity.

The above tentative rule does not necessarily apply to other biological activities. Thus, the axial 1- α -7-dimethylamino-hexahydrocannabinol (8) causes intense yawning in monkeys, while the equatorial 1- β -7-dimethylamino-hexahydrocannabinol (9) is inactive. Neither (8) nor (9) are cannabimimetic (Ederly et al. 1984).

SUBSTITUTION ON C-1, C-2 VERSUS SUBSTITUTION ON C-1, C-6

Two groups of THC-type cannabinoids have been synthesized which differ only in that the chemical groupings in one of them at C-1, C-2 are situated at C-1, C-6 in the other (but retain their stereochemistry). They show almost equivalent cannabimimetic activity. Thus, 2- α -hydroxy-1- β -hexahydrocannabinol (10) is essentially inactive, as is 6- α -hydroxy-1- β -hexahydrocannabinol (11); 2- β -hydroxy-1- α - and 6- β -hydroxy-1- α -hexahydrocannabinol (12 and 13, respectively) are also inactive. However, both 2- α -hydroxy-1- α -hexahydrocannabinol (14) and 6- α -hydroxy-1- α -hexahydrocannabinol (15) are active at the same dose levels (Mechoulam et al. 1980).

A biochemical rationalization of the above data is not obvious at present.

SUBSTITUTION ON C-6 AND C-5

Several groups have compared the cannabimimetic activity of 6- β -hydroxy- Δ -1-THC (16) and 6- α -hydroxy- Δ -1-THC (17) (for a review, see Narimatsu et al. 1985). In man, the 6- β -epimer (16), in which the hydroxyl group is axial, is more active than (17); but the reverse has been observed in mice and rabbits, and they are equiactive in rhesus monkeys. Recently, the α -epimer (17) was again found to be less active than the 6- β -epimer (16) in a mouse catalepsy test but more potent in a test for hypothermia and equipotent in barbiturate synergism.

5-beta-Hydroxy-delta-6-THC (18) and 5-alpha-hydroxy-delta-6-THC (19) have been tested in rhesus monkeys only (Mechoulam et al. 1972). The 5-beta-epimer (18), in which the hydroxyl group is equatorial, was six to eight times less active than the 5-alpha-epimer (19), in which the hydroxyl group is axial.

The only conclusion that can be drawn (though somewhat fatuous) is that the level of cannabimimetic activity of THC's hydroxylated at some allylic positions seems to depend on the test used.

SUBSTITUTION ON THE SIDE CHAIN

A Pfizer group (Milne et al. 1980; Johnson and Melvin 1986) has found that diastereoisomer A (20) is at least 10 times more potent than its side chain counterpart, diastereoisomer B (21), in analgetic tests. As analgetic activity in this series parallels cannabimimetic activity, one can presume that the same ratio of activity will be observed in cannabimimetic tests.

Martin et al. (1984) have reported that (3"S)-3"-hydroxy-delta-1-THC (22) is circa (ca) five times more active than delta-1-THC and is about seven times more active than the R epimer (23) in THC discrimination in rats. Approximately the same ratio of activity was observed in dog ataxia tests; in hypothermia, (22) and (23) are surprisingly equiactive. However, Martin and coworkers pointed out that "calculation of exact potency ratios is complicated somewhat by the lack of absolute purity of the isomers."

3,4-CIS-THCs

Racemic 3,4-cis-delta-1-THC (24), racemic 3,4-cis-delta-6-THC (25), and (+)-3,4-cis-delta-1-THC appear to be essentially inactive in several animal tests (Edery et al. 1971; Uliss et al. 1975; Martin et al. 1981).

CANNABINOID ENANTIOMERS

Delta-3-THC

This cannabinoid in its racemic form was synthesized in the early 1940s. Although attempts were made then to obtain the enantiomers in a pure form, they were only partially successful. Recently, we were able to synthesize both (1S)-delta-3-THC (26), [α]D - 117° and (1R)-delta-

3-THC (27). $[\alpha]_D^{+114^\circ}$ with absolute optical purity (Srebnik et al. 1984). These enantiomers have now been tested in human volunteers (Hollister et al., in press). Subjects received progressively increasing intravenous doses of (1S)-delta-3-THC (26) and (1R)-delta-3-THC (27), beginning with 1 mg (in 1 ml ethanol) followed by progressive doubling of doses until definite effects were observed. Cannabimimetic effects with the (1S) epimer were noted at doses of 8 mg or higher. No effects were noted with the (1R) epimer. (1S)-delta-3-THC (26) is thus estimated to have a potency from one-third to one-sixth that of delta-1-THC.

The behavioral cannabimimetic effects observed with (1S)-delta-3-THC (26) were indistinguishable from those caused by delta-1-THC. As with delta-1-THC, an increase in the pulse rate was also noted. These experiments are the first ones with THC enantiomers in human subjects.

(-)-(3R,4R)-THCs versus (+)-(3S,4S)-THCs

The natural delta-1-THC and delta-6-THC have a (3R,4R) configuration and a negative rotation. The synthetic route, which was developed by our laboratory for delta-1-THC and delta-6-THC nearly 20 years ago (Mechoulam et al. 1967), makes possible also the synthesis of the unnatural (3S,4S) enantiomers as the starting material; verbenol (28) is available in both enantiomeric forms. This sequence has been widely used for the preparation of (+) cannabinoids and apparently is the only one still practical for the synthesis of (+)-delta-1-THC. (+)-Verbenol on condensation with olivetol leads to (29), which on ring opening leads to (+)-(3S,4S)-delta-6-THC (30), which can be converted with ease into (+)-(3S,4S)-delta-1-THC (31).

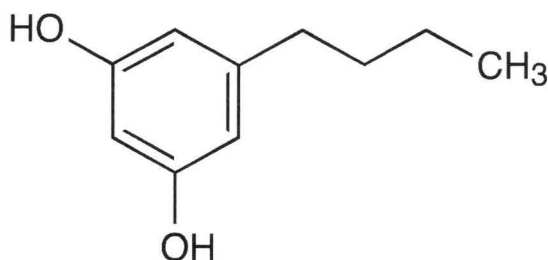
In several tests for cannabimimetic activity (Edery et al. 1971; Jones et al. 1974; Martin 1986), (+)-delta-1-THC (31) was ca 13 to 230 times less active than the (-)-isomer. These results indicate pharmacologic enantiomeric preference rather than absolute stereoselectivity. Indeed, Martin pointed out that, "while cannabinoid SAR supports the concept of a specific cannabinoid receptor, a disconcerting element is the apparent lack of greater stereoselectivity in some animal models." However, because the starting material (+) verbenol was not necessarily stereochemically pure, this conclusion is tentative at best.

Recently in our laboratories, we were able to prepare a pair of crystalline enantiomeric cannabinoids (compounds 32 and 33) which could be recrystallized to absolute enantiomeric purity. Their synthesis is based on myrtenol, which can be obtained in both enantiomeric forms.

The primary allylic group is first blocked as a pivalate ester (reaction a) (compound 34). If the blocking group is the more mundane acetate, the penultimate reaction (reaction e) proceeds in an undesirable fashion leading to the benzofuran (36). Oxidation of (34) leads to the crystalline ketone (35) which can be highly purified by crystallization. The synthetic sequence then follows the standard procedure described above, leading ultimately to the crystalline (+)-(3*S*,4*S*)-7-hydroxy-delta-6-THC-DMH (33). The configuration at C-3 and C-4 depends on the absolute configuration of myrtenol (-) myrtenol leads to the (-) enantiomer (32); (+) myrtenol leads to the (+) enantiomer (33).

Compounds (32) and (33) were tested in several independent cannabimimetic tests in Jerusalem, in Uppsala, and in Tucson. In all tests, the (-) enantiomer (32) exhibited potent cannabimimetic activity; the (+) enantiomer was inactive.

In Jerusalem, the compounds were examined in the mouse ring test. The (-) enantiomer (32) was ca 100 times more active than natural delta-6-THC: the ED₅₀ of delta-6-THC was 5 mg/kg; the ED₅₀ of (32) was 0.05 mg/kg. The (+) enantiomer (33) was inactive up to 20 mg/kg. In Tucson, the same type of results were observed in the rotorod neurotoxicity test in rats (see table 2). The (-)-enantiomer (32) was ca 260 times more potent than natural (-)-delta-6-THC; the (+)-enantiomer (33) was inactive at doses ca 2,000 times higher than those of the ED₅₀ of the (-)-enantiomer. In Uppsala, the compounds were tested in generalization tests with rats and pigeons. (-)-7-OH-delta-6-THC-DMH (32) was ca 87 times more active than natural delta-1-THC in the rat and ca 73 times more active in the pigeon (see table 3). The (+)-enantiomer (33) was inactive at doses ca 1,000 times and ca 4,500 times (for rats and pigeons, respectively) higher than those of the ED₅₀ of the (-) enantiomer (32).



5-Butylresorcinol

TABLE 2

Dose-Response Parameters of THC Stereoisomers in Rotorod (ROT) Neurotoxicity Tests in Rats (a)

Drug	ROT-TD50 (95% CL)
(-)-7-OH-delta-6-THC-DMH (32)	0.007 (0.005-0.009)
(+)-7-OH-delta-6-THC-DMH (33)	Not active (b)
(-)-delta-6-THC	1.85 (0.98-3.45)
(+)-delta-6-THC	21.66 (19.81-23.68)
(-)-delta-6-THC-DMH	0.034 (0.031-0.040)
(+)-delta-6-THC-DMH	0.53 (0.37-0.76)

a Median toxic (TD50) dose and 95% confidence limits (CL) are in mg/kg. b At 1.0, 7.0, and 15.0 mg/kg; higher doses were not tested due to insufficient quantity of drug.

TABLE 3

Generalization Tests with Various Doses of (-)-delta-1-THC, (-)-7-OH-delta-6-THC-DMH, and (+)-7-OH-delta-6-THC-DMH

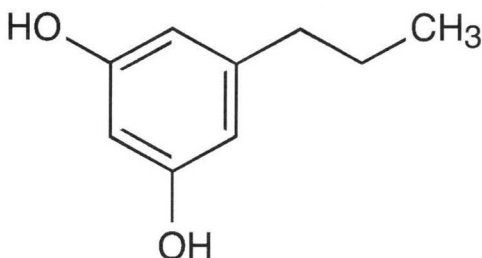
in Rats and Pigeons Trained to Discriminate Between the Presence and Absence of the Effects Induced by delta-1-THC

Compound	n	Dose Range (mg/kg)	Interval Range (hr)	ED50 (mg/kg)	r
(-)-delta-1-THC (R)	14	0.30-5.6	0.5-6.5	0.85	0.94
(-)-delta-1-THC (P)	7	0.10-0.56	0.5-9.0	0.16	0.91
(-)-7-OH-delta-6-THC-DMH (32) (R)	11	0.003-0.03	0.5-6.5	0.0098	0.99
(-)-7-OH-delta-6-THC-DMH (32) (P)	5-7	0.0001-0.0056	0.5-9.0	0.0022	0.99
(+)-7-OH-delta-6-THC-DMH (33) (R)	4-9	3.0- 10.0	0.5-6.5	>10.0	--
(+)-7-OH-delta-6-THC-DMH (33) (P)	4	3.0-10.0	0.5-9.0	>10.0	--

The animals, rats (R) and pigeons (P), were trained to discriminate between (-)-delta-1-THC (3 mg/kg, rats; and 0.56 mg/kg, pigeons) and vehicle administered 0.5-hr i.p. (rats) or 0.5-hr i.m. (pigeons) prior to session onset. The ED₅₀ values are based on the % RDP (percentage of responding to drug, THC, associated position) during the test probe yielding the highest % RDP, i.e., the lowest ED₅₀ value. *n* = the number of observations on which data points are based. ED₅₀ values refer to logarithmic regression analysis, and *r* refers to the correlation coefficient for the regression. The solubilization vehicle consisted of 5% (v/v) of propylene glycol, 2% Tween-80 (v/v), and 93% saline. In some cases, 4% Tween-80 and 91% saline were used.

The above results show that (-)-7-hydroxy-delta-6-THC-DMH (32) is one of the most active cannabimimetic substances prepared so far and that, apparently, cannabimimetic activity resides exclusively in the (-)-(3*R*,4*R*)-enantiomer. We assume that the results with the enantiomers (32) and (33) are also valid for the enantiomers of delta-1-THC, i.e., that our results are of a general nature. This assumption is based on the well-documented increase of cannabimimetic activity on the exchange of the pentyl chain with a DMH chain and on hydroxylation of the C-7 methyl group, which are the two features present in (32) and (33) and absent in delta-1-THC.

The results of animal tests of the types described above with delta-1-THC, delta-6-THC, and other cannabinoids have been shown to parallel activity in man (Hollister 1974). Hence, we assume that the results with (32) and (33) likewise indicate parallel activity in man. If this correct, cannabimimetic activity in man has a strict stereochemical requirement, which indicates a probable interaction with a chiral biological system (enzyme, receptor site, etc.) and not just an unspecific action due to the high lipid solubility of the cannabinoids.



5-Propylresorcinol

ANALGETIC ACTION OF THE (+) ENANTIOMER (33)

As mentioned above, the cannabimimetic SAR does not necessarily parallel the SAR of cannabinoids for other biological or therapeutic effects. Indeed, we have found now that enantiomer (33), which (as noted above) does not cause cannabimimetic effects, is a potent analgetic particularly in the presence of cupric ions. In table 4, we present the results of several analgetic tests. In all tests, (33) shows activity at (or above) the potency level of morphine. However, as previously noted with delta-1-THC and other cannabinoids, the dose-response curve is not sharp (as with morphine) but flat. Surprisingly, the level of analgetic potency is retained over a period of 3 to 4 days. In some tests, activity actually falls beyond a certain concentration, the dose-response curve assuming an inverted U shape.

The above results show that it is possible to achieve complete dissociation between cannabimimetic effect and analgetic action. These preliminary results may be of considerable therapeutic value because cannabinoids generally lack many of the side effects of opiates, such as high addiction liability and respiratory depression.

SUMMARY

The SAR of cannabimimetic activity in the cannabinoid series are reviewed with emphasis on the stereochemical requirements. Some new results are presented. The most important are that a, in humans, (-)-(1S)-delta-3-THC is much more active than (+)-(1R)-delta-3-THC; and b, with the 7-OH-delta-6-THC DMH enantiomers (32) and (33), the activity in several animal species resides completely in the (-)-(3R, 4R) enantiomer (32). The difference between the two enantiomers being up to several thousand times. The (3R,4R)-enantiomer (32) is much more active than delta-1- or delta-6-THC in animal tests, the exact level of activity depending on the test employed. The cannabimimetically inactive (+)-(3S,4S) enantiomer (33) was shown to be a potent analgetic in several animal tests. Thus, a complete dissociation between the cannabimimetic and the analgetic effects in a cannabinoid has been achieved, apparently for the first time.

TABLE 4

(+) 7-Hydroxy- Δ^6 -THC-DMH (33) and Morphine: Comparative Doses Producing 50 Percent of the Maximum Possible Analgesic Effect

ME₅₀ (mg/kg sc) at Time of Estimated Peak Activity of Compound^{a,b}

Compound	Mouse (Sabra Strain)			Rat (Sabra Strain)		
	Paw ^c Clamp	Acetic Acid ^d Writhing	Hot ^e Plate	Tail ^f Clamp	Tail ^f Clamp	Hot ^e Plate
(+) 7-OH- Δ^6 -THC-DMH (33) ^g	0.9	0.2	0.1	0.8	4.9	0.3
Morphine HCL ^h	4.2	1.3	1.6	4.3	5.5	2.0

^aAll morphine injected animals observed 1 hr postinjection.

^bAll (+) 7-OH- Δ^6 -DMH injected animals observed 2 hr postinjection.

^cHaflner et al. (1929); an adaptation

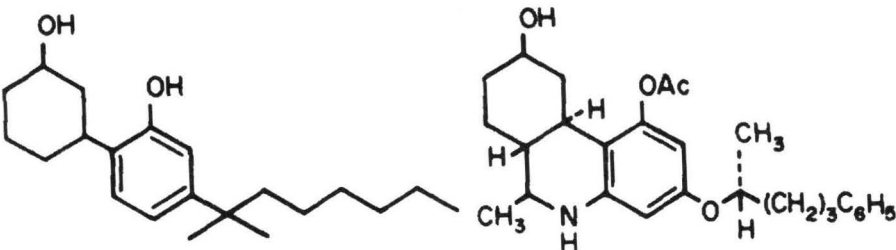
^dSophia et al. (1973)

^eWoolfe and MacDonald (1944)

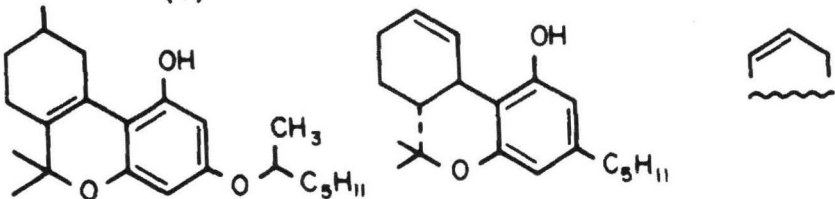
^fBianchi and Franceschini (1954)

^gDissolved in 5% EtOH, 5% emulphor 620, and 90% ddH₂O, with 5x10⁻⁴M CuCl₂ added subsequently.

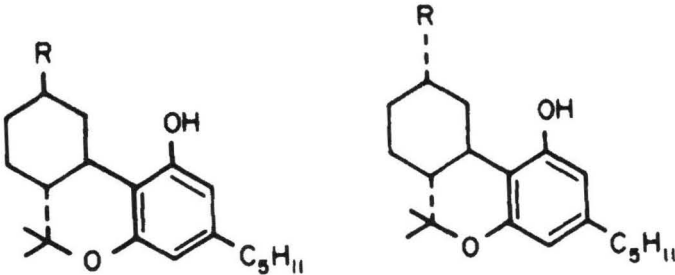
^hDissolved in 0.9% saline.



(1) (2)

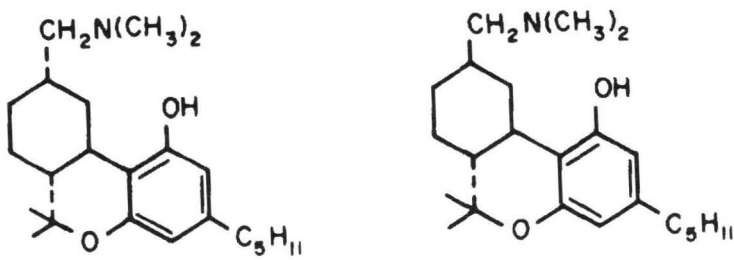


(3) (4) (5)

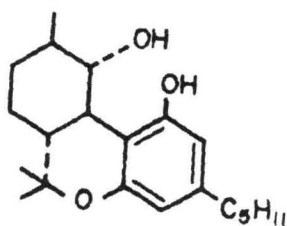


(6) (7)

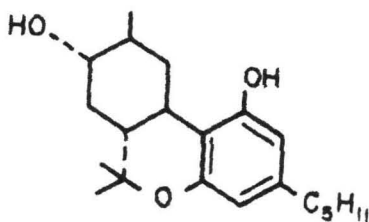
a, R = CH₃
b, R = CH₂OAc
c, R = CH₂OH



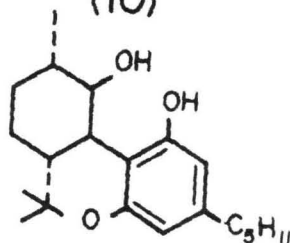
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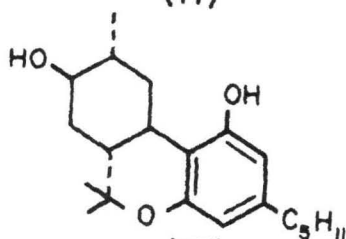
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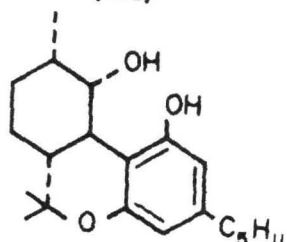
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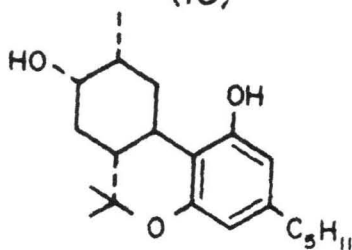
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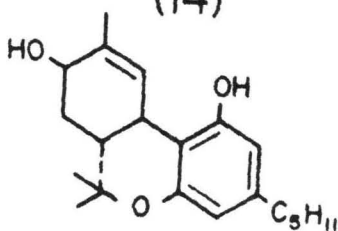
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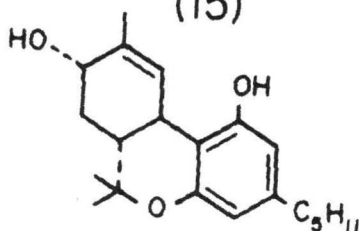
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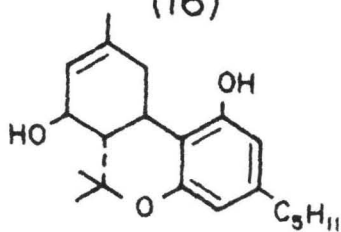
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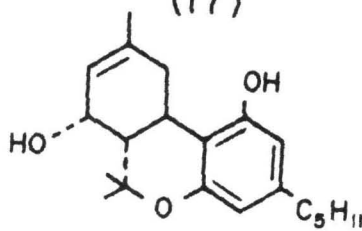
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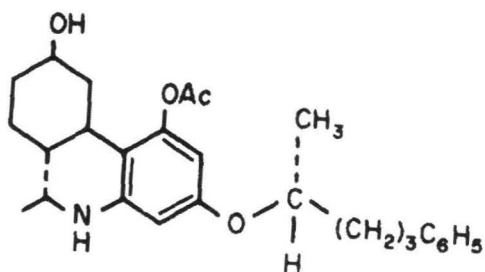
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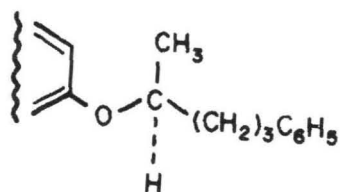
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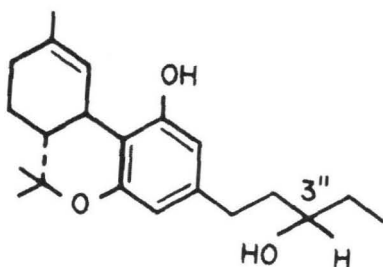
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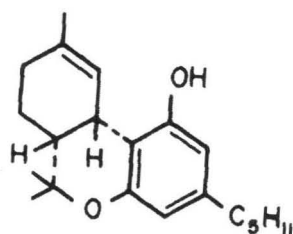
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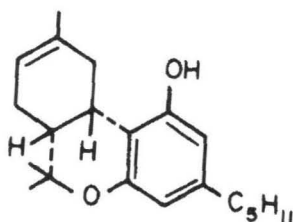


(22), 3''S

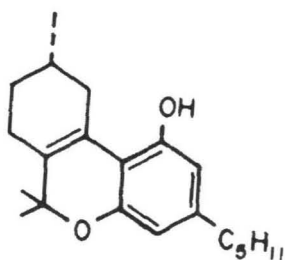


(23), 3''R

(24)

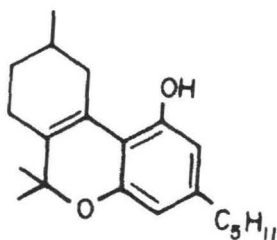


(25)



(1S)- Δ^3 -THC

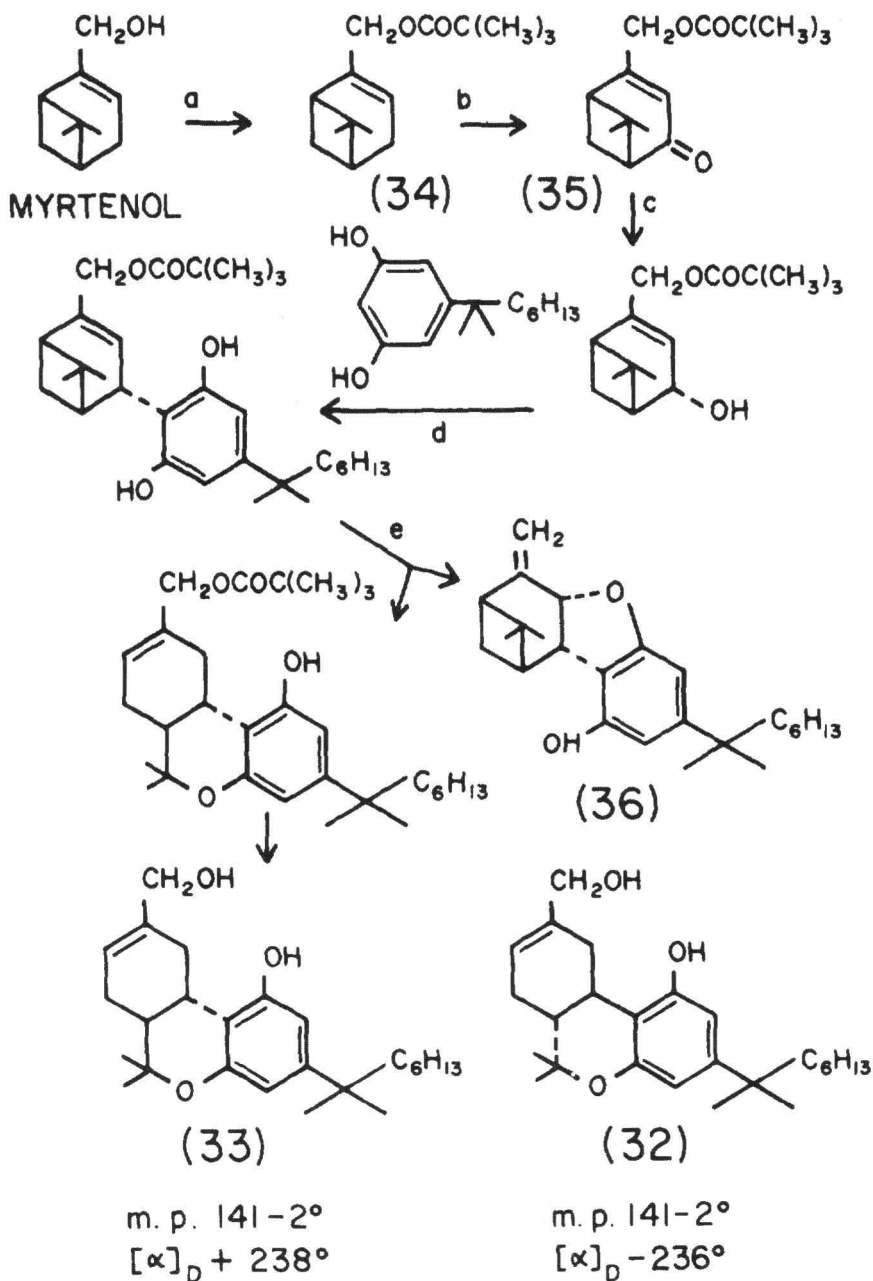
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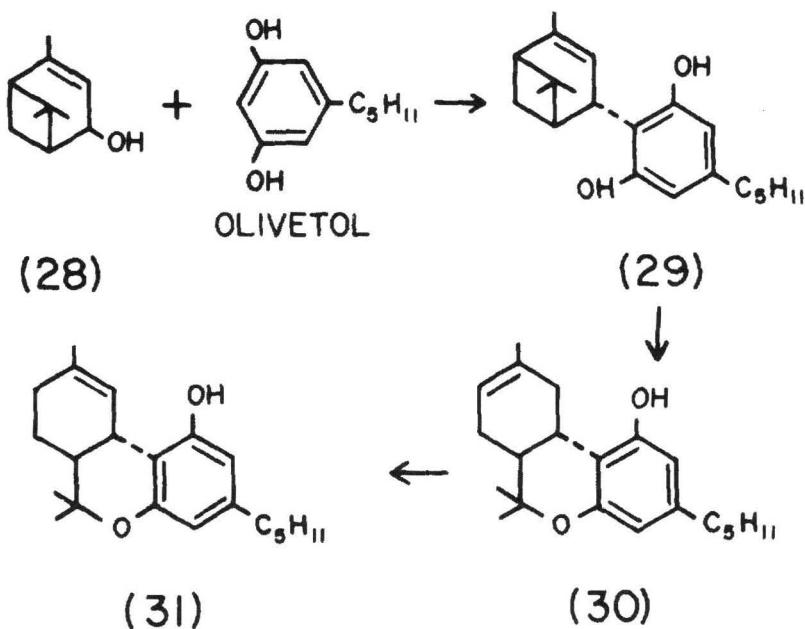


(1R)- Δ^3 -THC

(27)

SYNTHESIS OF 7-OH- Δ^6 -THC-DMH



SYNTHESIS OF (+)- Δ^1 -THC

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Chapter 3: Cannabinoid Receptors

by Francesco Della Valle; Alberta Leon;

Gabriele Marcolongo; Silvana Lorenzi

Padua, IT

September 30, 1997

Cannabinoids are a specific class of psychoactive compounds present in Indian *cannabis* (*Cannabis sativa*), including about 60 different molecules, the most representative being cannabinol, cannabidiol and several isomers of tetrahydrocannabinol. Knowledge of the therapeutic activity of cannabis dates back to the ancient dynasties in China, where, already 5,000 years ago, cannabis was used for the treatment of asthma, migraine and some gynaecologic disorders. Said use later became so established that about in 1850 cannabis extracts were included in the *US Pharmacopoeia* and remained therein until 1947.

Cannabinoids are able to cause different effects at the level of various systems and/or organs; the most important effects occur on the central nervous system and on the cardiovascular system. In fact, they are able to affect mood, memory, motor coordination and cognition, and they increase heart rate and variate the systemic arterial pressure. Furthermore, it is well known the capability of cannabinoids to reduce intraocular pressure and to affect the respiratory and endocrine systems (L. E. Hollister, Health Aspects of Cannabis, *Pharmacological Reviews*, 38, 1-20, 1986). More recently, it was found that they suppress the cellular and humoral immune response and have antiinflammatory properties (A. W. Wirth et al., Antiinflammatory Properties of Cannabichromene, *Life Science*, 26, 1991-1995, 1980).

The well established use of cannabis over the centuries, the mechanism of the effects of cannabinoids has been unknown until very recently. It was only in 1990 that Matsuda and collaborators identified and cloned a cannabinoid receptor belonging to the G-protein-coupled family of receptors; CB1 is coupled to G1 to inhibit adenylate cyclase activity and to a pertussis-sensitive G protein to regulate Ca²⁺ currents. Said receptor was found to be mainly located in the brain, in neural cell lines and only to a lesser extent at a peripheral level; therefore, in view of its localization, it was called Central Receptor (CB1) (Matsuda et al., Structure of a cannabinoid receptor and functional expression of the cloned cDNA, *Nature*, 346: 561-564, 1990). The discovery of a receptor led to assume the existence of a specific endogenous ligand.

In fact, subsequent research led to the isolation from pig brain of a substance able to exert an agonist action, i.e. capable of binding to the cannabinoid central receptor in a competitive way. Said substance was identified by structural investigation and by comparison with the synthetic product and was found to be an amidic derivative of arachidonic acid, and more particularly arachidonylethanolamide, later called anandamide. The pharmacological characterization of said molecule provided evidence that anandamide possesses a profile of activity which is similar to, though less potent than, Delta-9-THC (tetrahydrocannabinol with a double bond in position 9), and is capable of mimicking the psychoactive effects thereof. Said evidences led to the conclusion that anandamide is the endogenous ligand of the cannabinoid central receptor (C. C. Felder et al., Anandamide, an Endogenous Cannabimimetic Eicosanoid, Binds to the Cloned Human Cannabinoid Receptor and Stimulates Receptor-mediated Signal Transduction, *FNAS*, 90, 7656-7660, 1993; P. B. Smith et al., The Pharmacological Activity of Anandamide, a Putative Endogenous Cannabinoid, in Mice, *J. PET*, 270, 219-227, 1994).

Subsequent researches brought about the individuation of substances binding to CB1 receptor; said substances, which may be grouped into a class of amidic compounds, were denominated anadamides by the authors (L. Hanus et al., Two New Unsaturated Fatty Acids Ethanolamides in the Brain that Bind to the Cannabinoid Receptor, *J. Med.Chem.*, 36, 3032-3034, 1993). The discovery that the ethanolamide of arachidonic acid but not the ethanolamide of another biologically significant acid and anyway endogenously present in the brain such as palmitic acid, can functionally activate CB1 central receptor, brought about the subsequent identification of other amides of ethanolamine with highly unsaturated fatty acids, which have an affinity to CB1 receptor.

The multiplicity of effects of cannabinoids and CB1 receptor peculiar distribution led to assume the existence of differentiated receptor sites. In fact, a second different receptor for cannabinoids, called Peripheral Receptor (CX5 or CB2), was cloned. Being present in the spleen and macrophages/monocytes but absent at a central level, said receptor was regarded as responsible for mediating the cannabinoid-induced non-psychoactive effects (S. Munro et al., Molecular characterization of a peripheral receptor for cannabinoids, *Nature*, 365, 61-65, 1993). In this regard, the Delta-9-THC ability to induce immunosuppressive effects was proved. Recent experimental results showed that Delta-9-THC can cause alteration in the macrophagic function. In fact, the exposure to Delta-9-THC decreases the cytolytic activity of activated macrophages, measured as TNF- α synthesis, release and cytotoxicity. Moreover, since

macrophages release several cytolytic molecules, other than $\text{TNF-}\alpha$, they were supposed to be a target for Delta-9-THC (k. Fischer- Stenger et al., Delta-9-Tetrahydrocannabinol Inhibition of Tumor Necrosis Factor- α : Suppression of Post-translational Events, *J. PET*, 267, 1558-1565, 1993). All the above evidences and the preferential massive localization of CB2 receptor at the immune system level prove that said receptor plays a specific role in mediating the immune and antiinflammatory response to stimuli of a different nature, the bacterial and viral ones included.

It was also demonstrated that anandamide, the endogenous ligand of CB1 central receptor, can bind to CB2 receptor with an affinity about 30 times lower than to the central receptor; this suggests the existence of another endogenous ligand for said receptor, so far unidentified (L. L. Iversen, Medical uses of marijuana?, *Nature*, 365, 12-13, 1993). As already mentioned, the therapeutic use of cannabinoids as analgesic, anti-emetic, anticonvulsant, spasmolytic and antiglaucoma agents, and, as more recently found, as anti-inflammatory agents...

The investigations conducted to date on the pharmacological effects mediated by cannabinoid receptors show that the non-psychoactive effects of *Cannabis* derivatives are mediated by CB2 peripheral receptor. Furthermore, the CB2 receptor localization proves that said non-psychoactive effects, i.e. the effects on the immune system, the anti-inflammatory, myorelaxant and antinociceptive effects, as well as the effects on pressure systems, are mediated by said receptor.

The Applicant found that a class of N-acyl-alkanolamides, in particular N-acyl-monoethanolamides and N-acyl-diethanolamides, is able to act on mast cells as a local antagonist system according to a mechanism of autacoid type; therefore, such compounds can be conveniently used in the treatment of diseases connected with acute or chronic inflammatory events, such as for example autoimmune diseases. To said class of compounds belongs also N-(2-hydroxyethyl)-hexadecanamide, or N-palmitoyl-ethanolamide (N-PEA), a compound whose activity was discovered accidentally in the 1950's, following the identification of a generic cytoprotective activity of a lipidic excipient of an antirheumatic drug, which contained said compound. The pharmacological profile of such compound was later studied in experimental models of injury caused by various agents: the ability to increase the animal resistance to various bacterial toxins led to the subsequent pharmaceutical development of said compound. In fact, a pharmaceutical product was developed in Czechoslovakia in the form of tablets, suitable for preventing infections of the respiratory tract. Therefore, the Applicant found that the activity exerted by N-PEA and by the wide class of N-acyl derivatives described in the aforementioned patent applications does not limit to a generic

and modest cytoprotective activity, but said class of compounds plays a specific and important role in local inhibitory modulation of mast cell degranulation.

Such an activity allows the use of the compounds belonging to said class as drugs, exerting not only a generic cytoprotective action, but specifically a modulation of mast cell degranulation and, therefore, an inhibitory action on the autoaggressive effects in autoimmune diseases and on the cytotoxic and lesive effects of diseases of different etiology, connected with inflammations. Said compounds are, therefore, capable of inhibiting the uncontrolled release of preformed mast cell granules, containing several proinflammatory mediators and, in particular, preformed granules containing Tumour Necrosis Factor (TNF- α), a highly cytotoxic cytokine involved in the autoaggressive autoimmunity process (R. Toms et al., *J. Neuroimmunology*, 30, 169-177, 1990; P. G. Kruger et al. *Acta Neurol.Scand.*, 81, 331-336, 1990), as well as in lesive processes at the level of different tissues and organs.

Source: Della Valle 1999

CB2 Agonist in the Treament of Autoimmunine Disorders

by Alexandros Makriyannis of Willimantic, CT;
Atmaram Khanolkar and Dai Lu of Storrs, CT
May 4, 1999

Delta-8-Tetrahydrocannabinol, the psychoactive marijuana derived cannabinoid, binds to the CB1 receptor in the brain and to the CB2 receptor in the spleen. Activation of the CB2 receptor has been shown to result in suppression of the immune system (Mechoulam, *Cannabinoids as Therapeutic Agents*, CRC Press, Boca Raton, Fla. (1986)). Thus, drugs which selectively activate the CB2 receptor have great potential as immunomodulatory agents for preventing tissue rejection in organ transplant patients and as immunosuppressive agents for treating autoimmune associated diseases, (e.g., lupus erythematosus, rheumatoid arthritis, psoriasis, multiple sclerosis and inflammatory bowel diseases such as ulcerative colitis and Crohn's disease). CB2 receptor agonists also can be used as anti-inflammatory agents and as agents for suppressing peripheral and idiopathic pain. Source: Makriyannis 2000

CB-2 Receptor Agonist Compounds

by Murielle Rinaldi of Saint Georges d'Orques, FR; Francis Barth Montpellier, FR; Pierre Casellas of Montpellier, FR; Christian Congy of Saint Gely du Fesc, FR; Didier Oustric of Le Cres, FR; Malcolm R. Bell of East Greenbusch, NY; Thomas E. D'Ambra of Rexford, NY and Richard E. Philion of Pottstown, PA

December 22, 1997

Delta-9-THC is the main active constituent extracted from *Cannabis sativa* (Tuner, 1985; in *Marijuana 1984*, Ed. Harvey, DY, IRL Press, Oxford). Numerous articles have described not only psychotropic effects of cannabinoids but also their influence on the immune function [Hollister L. E., *J. Psychoact. Drugs* 24 (1992) 159-164]. The majority of in vitro studies have shown that cannabinoids have immunosuppressant effects: inhibition of the mitogen induced proliferative responses of T lymphocytes and B lymphocytes [Luo, Y. D. et al., *Int. J. Immunopharmacol.* (1992) 14, 49-56; Schwartz, H. et al., *J. Neuroimmunol.* (1994) 55, 107-115], inhibition of the activity of cytotoxic T cells [Klein et al., *J. Toxicol. Environ. Health* (1991) 32, 465-477], inhibition of the microbicidal activity of macrophages and of TNF- α synthesis [Arata, S. et al., *Life Sci.* (1991) 49, 473-479; Fisher-Stenger et al., *J. Pharm. Exp. Ther.* (1993) 267, 1558-1565] and inhibition of the cytolytic activity and the TNF α production of large granular lymphocytes [Kusher et al., *Cell. Immun.* (1994) 154, 99-108].

In some studies, amplification effects have been observed, namely an increase in the bioactivity of interleukin-1 by mouse fixed macrophages or differentiated macrophagic cell lines, due to enhanced levels of TNF α [Zhu et al., *J. Pharm. Exp. Ther.* (1994) 25 270, 1334-1339; Shivers, S. C. et al., *Life Sci.* (1994) 54, 1281-1289].

The effects of cannabinoids are due to an interaction with high affinity specific receptors present in the central nervous system (Devane et al., *Molecular Pharmacology* (1988) 34, 605-613) and peripheral nervous system (Nye et al., *The Journal of Pharmacology and Experimental Therapeutics* (1985) 234, 784-791; 30 Kaminski et al., *Molecular Pharmacology* (1992) 42, 736-742; Munro et al., *Nature* (1993) 365, 61-65).

The central effects are dependent on a first type of cannabinoid receptor (CB1), which is present in the brain. Furthermore, Munro et al. [*Nature* (1993) 365, 61-65] have cloned a second cannabinoid receptor coupled to protein G, called CB2, which is present only in the peripheral nervous system and more particularly on the cells of immune origin. The presence of CB2 cannabinoid receptors on the lymphoid cells may

explain the immunomodulation, referred to above, which is exerted by cannabinoid receptor agonists. Source: Rinaldi 2000

Inhibition of Cell Proliforation

by B. Sumner H. Burstein; Lawrence D. Recht; and
Robert B. Zurier Boston, MA May 8, 2001

One of the activities associated with THC and some of its derivatives is inhibition of cell proliferation. However, this activity, as with psychoactivity, is dependent on binding to the cannabinoid receptor CB1 (Galve-Roperh et al., *Nat. Med.* 6:313-319, 2000; De Petrocellis et al., *Proc. Natl. Acad. Sci. USA* 95:8375-8380, 1998; and Bisogno et al., *Eur. J. Biochem.* 254:634-642, 1998). Thus, non-psychoactive derivatives of THC, which do not bind to the CB1 receptor (Burstein, *Pharmacol. Ther.* 82:87-96, 1999), are not expected to inhibit cell proliferation.

The invention is based on the discovery that non-psychoactive THC derivatives, such as THC acids, can decrease cell proliferation. Moreover, this effect is not dependent on an increase in the rate of apoptosis, which has been identified as a CB1 receptor-mediated activity of THC (Sanchez et al., *FEBS Lett.* 436:6-10, 1998).

Source: Burstein 2002

Cannabinoids in the Treatment of Glaucoma

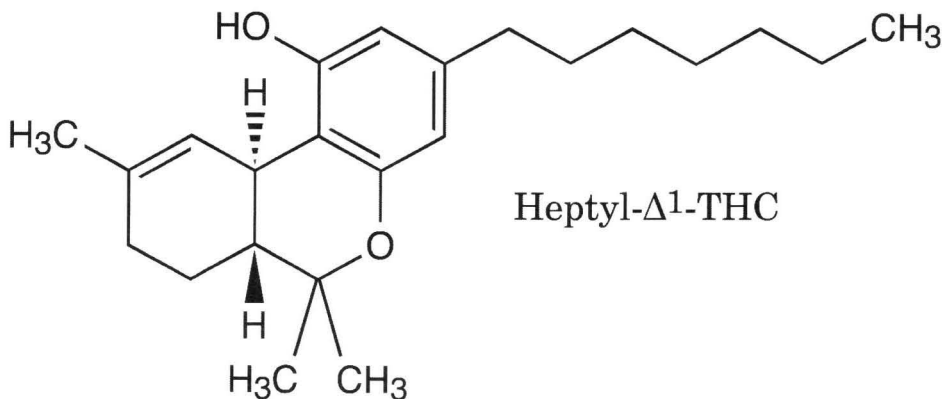
by David W. Pate of Amsterdam, NL;
Tomi Jarvinen of Kuopio, FI;
Kristina Jarvinen of Kuopio, FI;
Arto Urtti of Mill Valley, CA July 10, 1995

Subjects who smoke marijuana have reduced intraocular pressure (Helper et al, *J. Am. Med. Assoc.*, 217:1392 (1971)). The primary psychoactive ingredient in marijuana is known to be delta-9-tetrahydrocannabinol ("THC"). Human experiments involving intravenous administration of pure THC have confirmed the intraocular pressure reduction phenomenon seen with subjects who smoke marijuana (Cooler et al, *South. Med. J.*, 70:954 (1977)). As a result, cannabinoids have been investigated as anti-glaucoma agents. Source: Pate, D.W.; Anandamide analog compositions and method of treating intraocular hypertension using same; (1999) Source: Pate 1999

Anandamide Amidase Inhibitors as Analgesic Agents

by Alexandros Makriyannis of Ashford, CT
 Sonyan Lin of Storrs, CT
 William Adam Hill of Ashford, CT
 November 12, 1997

Delta-9-Tetrahydrocannabinol, the psychoactive marijuana derived cannabinoid, binds to the CB1 receptor in the brain and to the CB2 receptor in the spleen. Compounds which stimulate the CB1 receptor have been shown to induce analgesia and sedation, to cause mood elevation, to control nausea and appetite and to lower intraocular pressure (Mechoulam, *Cannabinoids as Therapeutic Agents*, CRC Press, Boca Raton, Fla. (1986), Fride and Mechoulam, *Eur. J. Pharmacol.* 231:313 (1993), Crawley et al., *Pharmacol. Biochem. Behav.* 46:967 (1993) and Smith et al., *J. Pharm. Exp. Therap.* 270:219 (1994)). Cannabinoids have also been shown to suppress the immune system (Mechoulam, *Cannabinoids as Therapeutic Agents*, CRC Press, Boca Raton, Fla. (1986). Thus, compounds which stimulate the CB1 or CB2 receptor, directly or indirectly, are potentially useful in treating glaucoma, preventing tissue rejection in organ transplant patients, controlling nausea in patients undergoing chemotherapy, controlling pain and enhancing the appetite and controlling pain in individuals with AIDS Wasting Syndrome.
 Source: Makriyannis 1999



CB1 Agonists for Use in Brain Trauma

by Joachim Mittendorf of Wuppertal, DE; Jurgen Dressel of Radevormwald, DE; Michael Matzke of Wuppertal, DE; Jurgen Franz Haan, DE; Peter Spreyer of Dusseldorf, DE; Verena Vohringer of Wuppertal, DE; Joachim Schuhmacher of Wuppertal, DE; Arno Friedl of Bergisch Gladbach, DE; Ervin Horvath of Leverkusen, DE; Frank Mauler of Overath, DE; Jean-Marie-Viktor De Vry of Rosrath, DE and Reinhard Jork of Overath, DE

February 17, 1998

Delta-9-Tetrahydrocannabinol (Delta-9-THC) and, to a small extent, also Delta-8-THC are the biologically active constituents in extracts of the plant *Cannabis sativa* (marihuana, hashish) and are responsible for the effects on the human central nervous system (CNS). Potential historical and contemporary therapeutic uses of cannabis preparations include, inter alia, analgesia, emesis, anorexia, glaucoma and motor disorders.

It is additionally known that cerebral apoplexy is a result of a sudden circulatory disorder of a human brain area with subsequent functional losses, with corresponding neurological and/or psychological symptoms. The causes of cerebral apoplexy can lie in cerebral haemorrhages (e.g. after a vascular tear in hypertension, arteriosclerosis and apoplectic aneurysms) and ischaemias (e.g. due to a blood pressure drop crisis or embolism).

The functional losses in the brain lead to a degeneration or destruction of the brain cells (cf. *Journal of Cerebral Blood Flow and Metabolism* 1981, 1, 155; *Chem. Eng. News* 1996 (May 13), 41; *Trends Pharmacol. Sci.* 1996, 1, 227). Craniocerebral trauma is understood as meaning covered and open cranial injuries with involvement of the brain [cf. *Schweiz. med. Wschr.* 1993, 123 449].

After a cerebral vascular occlusion, only a part of the tissue volume is destroyed as a direct result of the restricted circulation and the decreased oxygen supply associated therewith [cf. *Neurology* 1996, 47, 884]. This tissue area designated as the infarct core can only be kept from dying off by immediate recanalization of the vascular closure, e.g. by local thrombolysis, and is therefore only limitedly accessible to therapy. The outer peripheral zone, which is at least just as large in terms of volume, also designated as the penumbra, admittedly also discontinues its function immediately after onset of the vascular occlusion, but is initially still adequately supplied with oxygen by the collateral supply and irreversibly damaged only after a few hours or even only after days.

Since the cell death in this area does not occur immediately, a therapeutic opportunity reveals itself to block the unfavourable development of the course of the disease both after stroke and after trauma.

It has now been found that the known cannabinoid CB1 receptor agonists cited above are surprisingly suitable for the prophylaxis and treatment of neurodegenerative disorders, in particular of cerebral apoplexy and craniocerebral trauma. Source: Mittendorf 2001

Erratic Gastrointestinal Absorbtion of delta-9-Tetrahydrocannabinol

by Mahmoud A. Elsohly of Oxford, MS;
Samir A. Ross of Oxford, MS and
Shixia Feng of Oxford, MS October 26, 1998

Delta-9-tetrahydrocannabinol (THC, also known as Dronabinol) is the main biologically active component in the *Cannabis* plant which has been approved by the Food and Drug Administration (FDA) for the control of nausea and vomiting associated with chemotherapy and, more recently, for appetite stimulation of AIDS patients suffering from the wasting syndrome. The drug, however, shows other biological activities which lend themselves to possible therapeutic applications, such as in the treatment of glaucoma (ElSohly 1984), migraine headaches (El-Mallakh 1987, Volfe 1985), spasticity (Maurer 1990), anxiety (McLendon 1976), and as an analgesic (Maurer 1990). It is because of these-promising biological activities of THC that marijuana has been brought into a public debate relative its medicinal value.

The balance between medicinal use of a drug and the abuse potential is a delicate balance. One of the main points brought by the medicinal marijuana proponents is the fact that the currently available soft gelatin capsule formulation is very expensive and lacks consistency in its effects. The latter point could be explained based on the fact that oral THC has erratic absorption from the gastrointestinal tract, is subject to the first-pass effect resulting in heavy metabolism with production of high levels of 11-OH-THC, and undesirable side effects.

Source: Elsohly 1999

Treating Mental Diseases, Inflammation and Pain with Anandamides

by Daniele Piomelli and Massimiliano Beltramo
San Diego, CA December 6, 1996

Anandamide (N-arachidonylethanolamine) is thought to act as an endogenous cannabinoid neurotransmitter in vertebrate nervous systems. It binds to and activates cannabinoid receptors and simulates many distinctive effects typical of plant-derived or synthetic cannabinoid drugs.

Biochemical evidence indicates that anandamide is produced in and released from neurons in an activity-dependent manner. Further, as expected of a signalling molecule, anandamide is short-lived: its life-span is limited by uptake into neural cells and by enzymatic hydrolysis. Anandamide hydrolysis is catalyzed by the enzyme anandamide amidohydrolase, which converts anandamide to yield two inactive metabolites, arachidonate and ethanolamine.

Anandamide amidohydrolase is likely to play an important role in the physiological degradation of anandamide. Three lines of evidence support this possibility. First, anandamide amidohydrolase is highly selective. Second, anandamide amidohydrolase is discretely distributed in the central nervous system, where its localization parallels that of cannabinoid receptors.

Therefore, inhibition of anandamide amidohydrolase to increase the accumulation of anandamide at its sites of action is desirable as a potential therapeutic approach for the treatment or prevention of disorders such as mental diseases, inflammation and pain, including treatment or prevention of schizophrenia, mood disorders, anorexia, multiple sclerosis, spasticity and glaucoma. Source: Piomelli 1999

Chapter 4: Cannabinoid Extraction

by G. R. Barrie Webster of Winnipeg, CA

Leonard P. Sarna; Ste. Anne, CA January 24, 2000

Recently, public interest in *Cannabis* as medicine has been growing, based in no small part on the fact that *Cannabis* has long been considered to have medicinal properties, ranging from treatment of cramps, migraines, convulsions, appetite stimulation and attenuation of nausea and vomiting. In fact, a report issued by the National Academy of Sciences' Institute of Medicine indicated that the active components of *Cannabis* appear to be useful in treating pain, nausea, AIDS-related weight loss or "wasting", muscle spasms in multiple sclerosis as well as other problems. Advocates of medical marijuana argue that it is also useful for glaucoma, Parkinson's disease, Huntington's disease, migraines, epilepsy and Alzheimer's disease.

Marijuana refers to varieties of *Cannabis* having a high content of $\Delta 9$ -tetrahydrocannabinol ($\Delta 9$ -THC), which is the psychoactive ingredient of marijuana whereas industrial hemp refers to varieties of the *Cannabis* plant that have a low content of $\Delta 9$ -THC.

The controversy regarding the medicinal use of marijuana is centered not only on what is delivered but on how it is delivered. Specifically, the primary method used to deliver marijuana into a patient's system is by smoking the marijuana; however, smoking increases an individual's risk for cancer, lung damage and emphysema. Furthermore, as discussed above, marijuana does contain high levels of a psychoactive drug, $\Delta 9$ -THC. As such, there has been considerable debate as to whether or not the potential health benefits of smoking marijuana outweigh the health benefits.

In the example described herein, industrial hemp is harvested and the hemp seeds are threshed from the chaff. The chaff is collected and may then be dried or extracted green. In the embodiment described herein, the chaff is dried and is then finely divided, ground or pulverized. The ground chaff is then extracted with a solvent. In this embodiment, the time of residency of the ground chaff in the solvent is up to approximately 2-4 hours. Furthermore, the mixing ratio of chaff to solvent is such that the chaff can be suspended in the extracting medium during the extraction process. Specifically, in this embodiment the volume ratio is between 10:1 to 100:1. The solvent may be an organic solvent, for example, a petroleum derived hydrocarbon such as for

example toluene or trimethylpentane, a low molecular weight alcohol such as for example ethanol, or a low molecular weight chlorinated hydrocarbon such as for example dichloromethane. As will be appreciated by one knowledgeable in the art, other suitable solvents known in the art or combinations thereof may also be used, and the time of residency, volumes and mixing ratios may be varied based upon the cannabinoid(s) to be extracted. In some embodiments, the extract may be concentrated by evaporation of the solvent.

It is of note that in some embodiments, the specific cannabinoids isolated are those cannabinoids with suspected health benefits or suspected medicinal uses. For example, the cannabinoids and cannflavins may be used as anti-emetics, antinauseants, appetite stimulants, anti-inflammatories, antioxidants, neuroprotectives, analgesics, suppressants for primary immune response, glaucoma remedies, antineoplastics, migraine headache remedies, menstrual pain remedies, anticonvulsants, anti-epileptics, or movement disorder remedies. The essential oils may be used for aromatherapy or as flavoring/scenting adjuvants.

Source: Webster 2002

Extraction of Delta-9-Tetrahydrocannabinol from *Cannabis*

by Mahmoud A. Elsohly of Oxford, MS (US)
and Samir A. Ross of Oxford, MS (US)

October 26, 1998

Delta-9-tetrahydrocannabinol (THC, also known as dronabinol) is the main biologically active component in the *Cannabis* plant which has been approved by the Food and Drug Administration (FDA) for the control of nausea and vomiting associated with chemotherapy and, more recently, for appetite stimulation of AIDS patients suffering from the wasting syndrome. The drug, however, shows other biological activities which lend themselves to possible therapeutic applications, such as in the treatment of glaucoma (1), migraine headaches (2,3), spasticity (4), anxiety (5), and as an analgesic (4). It is because of these-promising biological activities of THC that marijuana has been brought into a public debate relative its medicinal value. The balance between medicinal use of a drug and the abuse potential is a delicate balance. One of the main points brought by the medicinal marijuana proponents is the fact that the currently available soft gelatin capsule formulation is very

expensive and lacks consistency in its effects. The latter point could be explained based on the fact that oral THC has erratic absorption from the gastrointestinal tract, is subject to the first-pass effect resulting in heavy metabolism with production of high levels of 11-OH-THC, and undesirable side effects.

Several investigations have been carried out over the years to isolate THC from the plant material, mostly to determine its chemical structure or to investigate the phytochemistry of the plant. In 1942, Wollner, et al., (11) reported the isolation of tetrahydrocannabinol from cannabis extract "red oil". Red oil was prepared by extraction of the plant material with ether, followed by distillation of the concentrated extract at room pressure followed by redistillation under reduced pressure (15-50 mm Hg).

The plant material is extracted with a non-polar organic solvent. Useful solvents include lower alkanes, such as, for example, hexane, heptane or iso-octane. The extract containing THC, after solvent removal, is subjected to fractional distillation under reduced pressure and a first distillate is collected. In one embodiment of the present invention, the first distillate is again subjected to fractional distillation at reduced pressure and a second distillate is collected. The second distillate has a THC content of greater than 90% by wt.

Extraction of *Cannabis* Buds 41% THC Oil

One kg of the fine powdered marijuana plant material [average % of THC was about 5.21%] was macerated with 6 L. hexanes (Hexanes GR from EM Sciences) in a percolator (9" in diameter from the top and 20" long, cone shaped) for 24 hours at room temperature and filtered. The macerate was reextracted with 5 L. hexanes for another 24 hours. The hexane extracts were combined and evaporated under reduced pressure at low temperature to give 110.7 g residue (11.07% extractives). The % of THC in the hexane extract was 41.21%.

Extraction of Cannabis Buds 2

40% THC Oil

One kg of the fine powdered marijuana plant material [average % of THC is 4.42] was macerated with 6 L hexanes and extracted by the same procedure followed in Example 3 to yield 105.8 g residue (10.58% extractives). The % of THC in the hexane extract was 40.35% by GC analysis.

Direct Fractional Distillation

of the Hexane Extract

92% THC Oil

A portion (23.0 g) of the hexane extract was subjected to fractional distillation under reduced pressure (vacuum, 0.1-0.2 mm/Hg). The temperature was raised slowly to 160° C. where a small amount of material (<1 g) was collected and left separate. The major fraction (10.1 g) was collected between 170 and 180° C. GC analysis of this fraction showed 72.66% THC concentration.

A second portion (25.0 g) of the hexane extract was subjected to fractional distillation under similar conditions as the first portion. The major fraction collected between 170-180° C. weighed 11.6 g and had a THC concentration of 73.62%.

A third portion (25.0 g) of the hexane extract was subjected to fractional distillation under similar conditions to the previous portions. The major fraction containing THC weighed 10.2 g and had a THC concentration of 73.72%.

The three major fractions obtained from the above three distillations were combined and analyzed. The analysis showed the concentration of THC to be 70.31%. The mixture (28.9 g) was subjected to fractional distillation, again under similar conditions. The temperature was raised slowly to 135° C. under vacuum (0.1-0.15 mmHg) and the fractions collected were kept aside. The major THC containing fraction was collected at 140-160° C. and 0.05-0.06 mm/Hg. The fraction weight was 18.4 g and the THC content was 92.15%. Source: Elsohly 2002

Preparing Delta-9-Tetrahydrocannabinol

by Mahmoud A. Elsohly of Oxford, MS (US)

Samir A. Ross of Oxford, MS (US) December 4, 2001

Direct Treatment of Cannabis Extracts with Methanolic KOH Solution 70% THC Oil

5.28 g of the heptane extract (THC content 41.4%) was sonicated very well with 50 mL. of 0.25 N KOH in methanol and filtered. The precipitate weighed 1 g (most probably hydrocarbons). The filtrate was acidified with 15 mL. of 1 N HCl and extracted twice with hexane (100 mL. x 2) to give 3.18 g residue (THC content 70.02%), with almost quantitative recovery.

Reprocessing of the Residue Left After Fractional Distillation of Cannabis Extracts 82% THC Yellow Oil

34 g of marijuana extract containing 55% of THC was distilled under vacuum (0.3 mmHg) and the distillate at 174-192° C. was collected to give 17.8 g of pale yellow oil that contained 82% THC.

The residue remaining in the distillation flask was cooled to room temperature and weighed 15.7 g which analyzed for 25% THC. This was triturated with 50 mL. of methanol and filtered. The filter cake was triturated with another 50 mL of methanol and filtered. The filtrates were combined and evaporated to give 7.04 g of oil which analyzed for 55% THC (98% recovery). Source: Elsohly 2002



Chapter 5: THC Syntheses

Water Soluble Derivatives of Cannabinoids

Billy R. Martin of Richmond, VA and
Raj K. Razdan Gloucester, MA May 29, 1998

Δ^9 -tetrahydrocannabinol (Δ^9 -THC) C.A. nomenclature!, which alternatively is often referred to as " Δ^1 -THC" where terpene series nomenclature is used, is the primary active ingredient of the plant *Cannabis sativa* (marijuana). Occasionally small quantities of the Δ^8 -THC isomer of Δ^9 -THC are also present in the plant. Both of these THC compounds have known pronounced pharmacological effects on mammals including humans. A wide variety of therapeutic applications of these THC compounds have been proposed or investigated, e.g., treatment of glaucoma, high blood pressure, anxiety states, insomnia, allergy, asthma, epilepsy, nausea, vomiting, ulcers, anorexia, pain (including migraine), and so forth, such as reported in *U.S. Pat. Nos.* 4,179,517 and 5,389,375. However, the formulation of Δ^8 - or Δ^9 -THC for medicinal uses has been problematic in view of the fact that these THC compounds are resinous gum materials which are insoluble in water. On the other hand, known solvents for these THC compounds, such as polyethylene glycol, alcohol, and so forth, tend to have pharmacological activity of their own, which is undesired. As a consequence, previous efforts to formulate Δ^8 - or Δ^9 -THC for pharmacological testing has been frustrated.

As an overview of Reaction Scheme 1, a Grignard reagent prepared from 4-bromophenoxybutane in tetrahydrofuran (THF) was treated with the nitrile compound (3) to produce the ketone compound (4) (85% yield).

i. Synthesis of Compound (4) Ketones from Nitriles

Now in more specific terms, the synthesis of 1-phenoxy-5-(3,5-dimethoxyphenyl)pentane (4) was accomplished as follows. To a mechanically stirred Grignard reagent (prepared from 91.6 g, 0.4 mmol of 4-bromophenoxybutane and 14.6 g, 0.6 mmol of magnesium turnings in 400 mL of anhydrous THF), added 48.9 g, 0.3 mmol of 3,5-dimethoxybenzonitrile (3) all at once and heated to reflux for 3 hours. The reaction was cooled to 0° C. with an ice bath for 15 minutes followed by the slow addition of 6N HCl (150 mL), and then allowed to stir at reflux over-

night. The THF was removed in vacuo and the residue dissolved in ethyl acetate (300 mL) and 6N HCl (50 mL). The layers were separated and the aqueous fraction extracted with ethyl acetate (4x150 mL). The combined ethyl acetate extract was washed with saturated NaHCO₃, followed by water and brine. After drying, it was concentrated and the residue was chromatographed on silica gel (650 g), eluting with 5%-25% ether/hexanes, to yield 79.8 g (85%) of compound (4). The product was compound (4) as confirmed by NMR analysis.

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Source: Martin 1998

NMDA-blocking pharmaceuticals

by Raphael Mechoulam of Jerusalem, IL; Mordechai Sokolovsky of Tel Aviv, IL; Yoel Kloog of Hertzlyia, IL; Anat Biegon of Tel Aviv, IL February 7, 1994

Pharmaceutical compositions are described for preventing neurotoxicity, crising as active ingredient the stereospecific (+) enantiomer, having (3S,4S) configuration of Δ^6 tetrahydrocannabinol type compounds. The compositions are particularly effective in alleviating and even preventing neurotoxicity due to acute injuries to the central nervous system, including mechanical trauma, compromised or reduced blood supply as may occur in cardiac arrest or stroke, or poisonings. They are also effective in the treatment of certain chronic degenerative diseases characterized by gradual neuronal loss.

Chronic degenerative changes, as well as delayed or secondary neuronal damage following direct injury to the central nervous system (CNS), may result from pathologic changes in the brain's endogenous neurochemical systems. Although the precise mechanisms mediating secondary damage are poorly understood, post-traumatic neurochemi-

cal changes may include overactivation of neurotransmitter release or re-uptake, changes in presynaptic or postsynaptic receptor binding, or the pathologic release or synthesis of endogenous factors. The identification and characterization of these factors and of the timing of the neurochemical cascade after CNS injury provides a window of opportunity for treatment with pharmacologic agents that modify synthesis, release, receptor binding, or physiologic activity with subsequent attenuation of neuronal damage and improvement in outcome. A number of studies have suggested that modification of post-injury events through pharmacologic intervention can promote functional recovery in both a variety of animal models and clinical CNS injury. Pharmacologic manipulation of endogenous systems by such diverse pharmacologic agents as anticholinergics, excitatory amino acid antagonists, endogenous opioid antagonists, catecholamines, serotonin antagonists, modulators of arachidonic acid, antioxidants and free radical scavengers, steroid and lipid peroxidation inhibitors, platelet activating factor antagonists, anion exchange inhibitors, magnesium, gangliosides, and calcium channel antagonists have all been suggested to potentially improve functional outcome after brain injury (Mcintosh, *J. Neurotrauma* 10: 215-243, 1993).

The pathogenesis of a diverse group of neurological disorders has been linked to excessive activation of excitatory amino acid receptors. These disorders include epilepsy, focal and global ischemia, CNS trauma, and various forms of neurodegeneration including Huntington's chorea, Parkinson's disease and Alzheimer's disease. There has been extensive effort invested in the development of excitatory amino acid receptor antagonists as therapeutic agents (Rogawski, M. A., *Trends in Pharmacol. Sci.* 14: 325-331, 1993).

Since no proven effective therapy for neuronal injury, or degeneration, is yet known, and, for example, stroke alone is one of the leading causes of death in many countries, the importance of finding such therapeutic NMDA antagonists is self-evident. It will be important to determine whether certain NMDA antagonists are more effective or have fewer side effects than others in specific disease states.

Some of the compounds of general formula (I) are disclosed in *U.S. Pat.* Nos. 4,179,517 and 4,876,276. As disclosed in said *U.S.* patents, these essentially pure synthetic (+)-(3S,4S)-THC derivatives and analogues are devoid of any undesired cannabimimetic psychotropic side-effects. These known compounds have been described as having analgesic, antiemetic and antiglaucoma activity.

The inventors have now found that the said known compounds, as well as some novel compounds, in addition to having said analgesic,

antiemetic and anti-glaucoma activity, are also effective against the diseases and conditions mentioned above, possibly as excitatory amino acid receptor blockers, for example NMDA- or glutamate-blockers or interaction with the glycine receptor, and are effective in the alleviation and treatment of many of the abnormal states involving said neurotransmitter mediated toxicity.

More references:

Mechoulam et al., *Tetrahedron Asymmetry* 1:315-319 (1990).

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Kloog et al., *Biochemistry* 27:843-848 (1988).

Mechoulam et al., *Experientia* 44:762-764 (1988).

Feigenbaum et al., *Pharmacol. Biochem. Behav.* 16:235-240 (1982).

Source: Mechoulam 1996

THC in the Treatment of Glaucoma in Patients who can not take Beta-blockers

by Harry G. Pars of Concord, Mass June 3, 1994

Glaucoma represents a significant health problem with estimates that between 2 to 9 percent of the adult population worldwide suffers from increased intraocular pressure. Current therapy include use of so-called "beta-blockers". These drugs however are not effective for all patients and often result in undesirable side effects that include lowered pulse rate, asthma and gastrointestinal problems. It thus would be desirable to have a new means for treatment of glaucoma.

Step 2. Synthesis of 2-(3',5'-dimethoxyphenol)-2-octanol (5)

The ketone 3 was converted to the alcohol 5 in practically quantitative yield by reaction with the Grignard reagent 4. Thus, a solution of 131.5 g (0.73 mol) of 3,5-dimethoxyacetophenone (3) in 175 mL of anhydrous diethyl ether was added during 25 minutes to a solution of the Grignard reagent, prepared in the normal way from 198.4 g (1.108 mols) of 1-bromoheptane (Aldrich) and 24.5 g (1.008 mols) of magnesium shavings, in 940 mL. of anhydrous diethyl ether. The initial temperature of the reaction mixture was 5° C. and the maximum temperature was 18° C. The cooling bath was removed at the end of the addition and the reaction mixture was heated at reflux for 30 minutes. By TLC (1:2 ethyl acetate/hexane, R_f = 0.47) there was no unreacted ketone at this point.

The cooled reaction mixture was poured in a thin stream into a vigorously stirred slurry of ice, solid ammonium chloride and 75 mL of concentrated hydrochloric acid. The alcohol 5 was recovered from the

washed and dried ether layer upon concentration in a rotary evaporator. The dark yellow oil (221.5 g) also contained the excess bromoheptane (17.9 g). The product showed two spots on TLC, the minor one being slower moving, but it was used in the next step without further purification.

Other References

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Source: Pars 1996

Compositions Useful as a Cannabinoid Receptor Probe

by Alexandros Makriyannis of Ashford, CT,

Guo Yan of Storrs, CT,

Vasiliki Abadji of Willington, CT August 6, 1993

Reggio, P. H., et al., "Characterization of a Region of Steric Interference at the Cannabinoid Receptor Using the Active Analog Approach," *J. Med. Chem.* United States, 36(12):1761-1771, (Jun. 11, 1993).

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branes Labeled with (3 H)-5'-Trimethylammonium Δ^8 -Tetrahydrocannabinol," *J. Pharmacol. Exp. Ther.*, 234(3):784-791 (1985).

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Various preparations of the plant *Cannabis sativa* have been used since ancient times for their behavioral and pharmacological properties. R. Mechoulam, *The Pharmohistory of Cannabis Sativa*, 1-19 (1986). More recently, it has been demonstrated that the active plant constituents, known as cannabinoids, produce a variety of effects including bronchodilation, increased heart rate, reduced intraocular pressure, analgesia, antiemesis, alteration in body temperature, as well as anticonvulsant and psychotropic activities. (W. L. Dewey, *Cannabinoid Pharmacology*, *Pharmacol. Rev.*, 38:45 (1986)).

Recent evidence supports the hypothesis that cannabinoids also produce some of their effects by interacting with specific protein sites in synaptosomal preparations and mammalian brains. (W. A. Devane et al., "Determination and Characterization of a Cannabinoid Receptor in Rat Brain", *Mol Pharmacol.*, 34:605-613 (1988), M. Herkenham et al., "Cannabinoid Receptor Localization in Brain", *Proc. Natl. Acad. Sci. USA*, 87:1932-1936 (1990)). For example, a cannabinoid receptor was shown to be more responsive to the psychoactive cannabinoids than the non psychoactive derivatives. (A. C. Howlett, "Cannabinoid Inhibition of Adenylate Cyclase Relative Activity of Constituents and Metabolites of Marihuana", *Neuropharmacology*, 26:507-512 (1987)).

Source: Makriyannis 1995

NMDA-blocking Pharmaceutical Compositions

by Yoel Kloog of Hertzlyia, IL; Jeffrey J. Feigenbaum
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Mordechai Sokolovsky of Tel Aviv, IL); Simon Benita
Mevasseret Zion, IL April 8, 1992

The present invention relates to pharmaceutical compositions for preventing excitatory amino acids neurotoxicity comprising as active ingredient (3S,4S)-tetrahydrocannabinol (THC) type compounds of general formula (I), as hereunder defined.

The compositions of the present invention are particularly effective in alleviating and even preventing glutamate neurotoxicity due

to acute injuries to the central nervous system (CNS), such as injuries due to prolonged seizures, compromised or reduced blood supply, deprivation of glucose supply and mechanical trauma. The present compositions may also be effective in alleviating other damages to the CNS like poison-induced convulsions, considered to be associated with amino acids receptors other than that of glutamate, for example glycine.

The compositions of the present invention are also effective in the treatment of certain chronic degenerative diseases which are characterized by gradual selective neuronal loss. In this connection, the compositions of the present invention are contemplated as therapeutically effective in the treatment of the Alzheimer's disease.

The present compositions are of special value in grand mal seizures, global hypoxic ischemic insults, in hypoxia, alone or in combination with blood flow reduction (ischemia) as well as in cases of cardiac arrest and in cases of abrupt occlusion of cerebral arteries (stroke).

Other References:

Mechoulam et al., *Tetrahedron Asymmetry* 1: 315-319 (1990).

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Kloog et al., *Biochemistry* 27: 843-848 (1988).

Mechoulam et al., *Experientia* 44: 762-764 (1988).

Feigenbaum et al., *Pharmacol. Biochem. Behav.* 16: 235-240 (1982).

Source: Kloog 1994

Production of 6,12-dihydro-6-hydroxy-cannabidiol and the use thereof for the production of *trans-delta-9-tetrahydrocannabinol*

by Peter Stoss of Illertissen, DE, Peter
Merrath of Memmingerberg, DE January 8, 1992

Cannabinoid compounds are components which can be isolated from *Cannabis* spp. Due to its physiological activity *trans-delta-9-tetrahydrocannabinol* (Δ^9 -THC) is of substantial significance. This compound is also referred to as 6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol.

The psychotropic but non-habit forming effects mean that this compound is of interest as pharmaceutical component.

The prior art discloses several different methods for the preparation of Δ^9 -THC. In conventional methods there is however the disadvan-

tage that known synthesis paths lead to a number of by-products, which are very difficult to separate from the desired final product. Furthermore the final product is obtained in the form of a resinous mass, something that is hardly conducive to simple purification. Due to these disadvantages production on an industrial scale meets with substantial difficulties.

The compound 6,12-dihydro-6-hydroxy-cannabidiol described in the present application has so far not been either synthetically produced or used as an intermediate for the production of *trans*-delta-9-tetrahydrocannabinol. One reference to it in the literature (see Garrett et al., *J. Pharm. Sci.* 67 (1978) pages 27-32) only relates to the analytical chromatographic trace detection of one of a number of many other products of decomposition of delta-9-THC in an acidic solution. The compound has therefore not been produced in preparative quantities nor used for any sort of reactions. Furthermore the physical data of the compound have not been described previous to the present application.

One object of the present invention is therefore to provide a method for the production of *trans*-delta-9-tetrahydrocannabinol both with a sufficient purity and also on an industrial scale.

In order to achieve this object firstly *trans*-delta-9-tetrahydrocannabinol is produced as an intermediate, which may be readily purified by crystallization. This intermediate is then converted by ring condensation to the desired delta-9-THC.

The method of production in accordance with the invention will be made clear by the following reaction scheme:

In accordance with the invention the first step is to produce the intermediate 6,12-dihydro-6-hydroxy-cannabidiol which may also be termed 1,3-dihydroxy-2-[6-(1-hydroxy-1-methyl-ethyl)-3-methyl-2-cyclohexene-1-yl]-5-pentyl-benzene. This compound is denoted I in the above scheme.

For the synthesis of 6,12-dihydro-6-hydroxy-cannabidiol as the intermediate in accordance with the invention the starting materials are the readily available olivetol (formula II) and *cis-p*-menth-2-ene-1,8-diol (formula III). The reaction is performed in a suitable solvent, aromatic hydrocarbons such as benzene and toluene, halogenated hydrocarbons such as methylene chloride, chloroform, dichloroethane and trichloroethane, ethers such as diethylether, diisopropylether and tetrahydrofuran having proved to be suitable. Furthermore it is possible to use mixtures of the said solvents. Toluene, benzene, methylene chloride and chloroform are the preferred solvents for use in the method of the invention.

Preferably the reaction in accordance with the invention is performed in the presence of a suitable catalyst, proton acids such as for instance haloid acids, sulfuric acid, phosphoric acid, perchloric acid, organic sulfonic acids, such as for instance methanesulfonic acid and *p*-toluenesulfonic acid, carboxylic acids, such as for instance oxalic acid, trifluoroacetic acid and other Lewis acids, such for instance boron trifluoride, ferric chloride, zinc chloride, zinc bromide, stannic chloride, titanium chloride or iodine having proved to be suitable. Furthermore mixtures of the individual catalysts may be used in certain cases.

Preferably hydrochloric acid and *p*-toluenesulfonic acid are used in accordance with the invention.

The method may be performed at temperatures between approximately -30° C. and +50° C., temperatures between 0° C. and 20° C. being preferred.

The reaction times are dependent on the solvent, the catalyst used and the reaction temperature. In fact it is possible to use reaction times between a few minutes and several hours.

The intermediate product produced may then be readily further purified by recrystallization. In this respect the use of petroleum ether has turned out to be suitable for the recrystallization.

Ring condensation may be used to produce the *trans-delta-9-tetrahydrocannabinol* (Δ^9 -THC) from 6,12-dihydro-6-hydroxy-cannabidol. This reaction is performed in a suitable solvent with the use of suitable catalysts and water binding substances. The solvent is in the form of a hydrocarbon, as for instance hexane, heptane, cyclohexane, petroleum ether, aromatic hydrocarbons, such as for instance benzene, toluene, chlorinated hydrocarbons, such as for instance methylene chloride, chloroform and dichloroethane. Preferably methylene chloride and chloroform are used. Furthermore mixtures of the solvents may be used.

As a catalyst for the ring condensation Lewis acids such as for instance zinc chloride, zinc bromide, boron trifluoride, ferric chloride, stannic chloride, titanium chloride or iodine are used, zinc chloride and zinc bromide having proved to be more particularly suitable. Water binding substances such as neutral substances as for instance magnesium sulfate, sodium sulfate, calcium sulfate or molecular sieves may be used, the last-named having proved more particularly suitable.

The reaction is performed at a temperature between approximately -20° C. and the boiling point of the corresponding solvent. The reaction times are dependent on the catalyst, the solvent, the water binding substance and the reaction temperature. Dependent on the selected conditions times from a few minutes to several days are required.

For the man in the art it will be clear that the reactions in accordance with the invention may be also performed using such functionalized derivatives as may also be used for the synthesis of Δ^9 THC.

It is an advantage in the method in accordance with the invention that starting with readily available materials the intermediate product in the form of 6,12-dihydro-6-hydroxy-cannabidiol may be produced simply with a good yield and that such product may be purified without any great difficulty.

Starting with the intermediate product in accordance with the invention it is possible to obtain highly pure, that is to say low-isomer Δ THC, the purification of the THC so obtained being possible by simple elution of a silica gel column. With the aid of the method described above it is possible to achieve a high, reproducible yield of the Δ^9 -THC and the production of the final product is also possible on an industrial scale.

Production of 6,12-dihydro-6-hydroxy-cannabidiol

90 g of olivetol were agitated with 85 g of *cis-p*-menth-2-ene-1,8,-diol and 4 g of *p*-toluenesulfonic acid H_2O in 4 L. methylene chloride for 24 hours at 20° C. Then extraction was performed once with 200 mL. of 4% calcium carbonate solution and the organic phase was reduced in vacuum to an oil. In this respect approximately 170 g of residue were obtained, which were dissolved in 1 L of petroleum ether (50/70) and extracted three times with respectively 300 mL. of 0.5 N sodium hydroxide.

The petroleum ether phase was then run into a silica gel column (approximately 500 g of silica gel) and eluted with a mixture of petroleum ether (50/70) and diisopropylether (2:1). The eluate was reduced in volume under vacuum and the residue (approximately 102 g) was recrystallized from 600 mL of petroleum ether (50/70). 77 g of the desired product were obtained. The characteristic data of the 6,12-dihydro-6-hydroxy-cannabidiol were as follows: Fusion point: 77° to 77.5° C.

Production of *trans*-delta-9-tetrahydrocannabinol

10 g of 6,12-dihydro-6-hydroxy-cannabidiol were dissolved in 300 mL of methylene chloride and held for 24 hours under reflux in the

presence of 20 g of zinc bromide and 15 g of molecular sieve 3. Then filtration was performed and the filtrate reduced in volume. The residue was taken up in 100 mL of petroleum ether and run into a silica gel column (approximately 100 g of the gel). Then elution was performed with petroleum ether and the eluate was reduced in volume. The residue obtained was Δ^9 -THC with a purity of greater than or equal to 96%.

Other References

Garrett et al., *Chemical Abstracts* vol. 88 (No. 22); p. 158340n (1978).
Stoss et al., *Chemical Abstracts*, vol. 115 (No. 17) p. 183602h (1991).
Tetrahedron Letters No. 8, pp. 681-684 (1979) Hendrick et al., "Hashish: Synthesis of . . . ". Source: Stoss 1993 Reference Stoss 1992

Preparation of *cis-p*-Menth-2-ene-1,8,-diol

Photoreaction on (+) limonene (orange oil) produces mixed isomers, first couple of fractions can be used to create active CB1 agonists see Schenck 1964. *cis-p*-Menth-2-ene-1,8,-diol and mixed isomers from a culture of *Penicillium italicum* and *P. digitatum* (moldy oranges) see Bowen (1975).

Novel tetrahydrocannabinol type compounds

by Raphael Mechoulam of Jerusalem, IL; Naphtali Landerof Tel-Aviv, IL; Shabtay Dikstein of Jerusalem, IL; Benyamin Shalita of Jerusalem, IL

December 28, 1976

The main psychotropically active compounds present in *Cannabis sativa* or in its preparations (marijuana, hashish, etc.) is (3R,4R)-(-)- Δ^1 -THC (I). Occasionally small quantities of the compound (3R,4R)-(-)- Δ^6 -THC (II) are found. Both compounds have a pronounced activity on mammals and on humans, producing the typical "*cannabis*" effect. This effect can be measured in animals in a quantitative manner by various tests, two of these being the monkey test, Grunfeld et al., *Psychopharmacol.* 14, 200 (1969) and by the ring test, Pertwee, *Brit. J. Pharmacol.* 46, 753 (1972). In the monkey test the minimum giving an effect is 50ug./kg of the (3R,4R)-(-)- Δ^1 -THC while that of (3R,4R)-(-)- Δ^6 -THC is 0.1 to 0.25 mg/kg.

In the ring test the above compounds are active at less than 1 mg/kg. There have been prepared various derivatives of the above compounds, having various different side-chains, see "*Marijuana*,

Chemistry, Pharmacology, Metabolism and Clinical Effects," R. Mechoulam (ed.), Academic Press, New York, 1973. Many of these possess the activity of the natural compounds, frequently at lower dosages and of longer duration, such as in the monkey test, 24 hours instead of 4 hours with the 1", 2"-(dimethylheptyl) homologue of (3R,4R)-(-) Δ^1 -THC (III). The corresponding Δ^6 -THC compound (IV) acts at 0.5 mg/kg for 30 hours.

Various cannabinoids, both natural and synthetic, have been examined for their therapeutic activity, see *Ann. Rev. Pharmacol.* 15, 210 (1975) and *Ann. Rep. Med. Chem.* 9, 253 (1974). These have shown that such compounds have a potential activity useful in the treatment of disorders such as glaucoma, high blood pressure, states of anxiety, insomnia, allergy, asthma, epilepsy, nausea, ulcers, pain (including migraine), etc. Due to the strong cannabis-type psychotropic activity of these compounds, which is a very pronounced and undesired side-effect, there is no possibility to make use of the useful pharmacological properties of the above defined compounds in view of the cannabis-type effects.

The novel compounds according to the present invention are substantially devoid of the undesired cannabis-type effects and can be used for the treatment of various diseases and disorders without undesired side-effects. As stated above, the novel compounds have an absolute stereochemistry at the 3- and 4-positions (terpene nomenclature) opposite to that of the natural series, i.e., they have a (3S,4S)-configuration. The compounds have a (+)-rotation of an absolute value approximately equal to that of the corresponding (-)-series compound.

For example, the 1", 2"-(dimethylheptyl)-homologue of (+)-(3S,4S)- Δ^6 -THC(Va) shows no activity in the monkey test up to 5 mg/kg. When tested on glaucomatic rabbits this compound is active in dilutions lower than 0.001% when administered directly into the eye in suspension. It has also a pronounced anti-ulcer activity. It is effective in the prevention and reduction of desoxycorticosterone and salt induced hypertension.

Other References:

Mechoulam et al., *JACS*, 94, 6159 (1972).

Jen et al., *JACS*, 89, 4551 (1967).

Mechoulam et al., *JACS*, 89, 4552 (1967).

Mechoulam et al., *JACS*, 87, 3273 (1965).

Yaoni et al., *JACS*, 86, 1646 (1964).

Fahrenholtz et al., *JACS*, 89, 5934 (1967).

Taylor et al., *JACS*, 88, 367 (1966).

Source: Mechoulam 1979

Preparation of (-)-6a,10a-trans-6a,7,8,10a- tetrahydrodibenzo[b,d]-pyrans

by Raj Kumar Razdan of Belmont, MA;
Haldean Cloyce Dalzell of Weston, MA

February 7, 1977

Cannabis preparations in the form of marihuana, hashish, etc. have been known and used for many years for their psychoactive and therapeutic properties. The major active constituent of the resin which is exuded by the female plants of *Cannabis sativa* L. is (-)-6a,10a-trans-1-hydroxy-3-n-pentyl-6,6,9-trimethyl-6a,7,8,10a-tetrahydrodibenzo[b,d]pyran, also known as (-)-6a,10a-trans- Δ -9-tetrahydrocannabinol or Δ 9-THC. The structure and absolute configuration of this material was first reported by Gaoni et al. in *J. Amer. Chem. Soc.*, 86, 1646 (1964). Since that time considerable research has been directed towards the preparation of this compound via a synthetic method, thereby eliminating the need to obtain the material by extraction from natural sources.

Because of the widespread use of *Cannabis* preparations all over the world, it has become necessary to study the pharmacology and toxicity of the active constituent, viz. Δ 9-THC in greater detail. In the past, attempts to study the pharmacological effects of this compound have been hampered by variations in the potency of the plant material. Accordingly, a supply of pure synthetic material is essential to carry out these studies as well as to enable accurately reproducible dosages of the active ingredient to be used for its pharmacological properties.

Example I

A mixture of 2.88 g (16.0 mmol) of olivetol, 2.45 g (16.1 mmol) of (+)-*cis/trans-p*-mentha-2,8-dien-1-ol, and 2 g of anhydrous magnesium sulfate was stirred with 100 mL of methylene chloride under N₂ atmosphere. After cooling in an ice bath, 1 mL (8.1 mmol) of freshly distilled boron trifluoride etherate was added. The mixture was stirred for 1.5 hr at 0° C and 5 g of anhydrous sodium bicarbonate was added. The stirring was continued until the color had faded, at which time the reaction mixture was filtered and evaporated to give a colorless gum (5 g). On the basis of gas-liquid chromatography, it contained 50 percent

of (-)-6a,10a-*trans*-1-hydroxy-3-*n*-pentyl-6,6,9-trimethyl-6a,7,8,10a-tetrahydrodibenzo[b,d]-pyran. One-half of this material was chromatographed on 150 g of magnesium silicate (100-200 mesh) packed in a 1 in. x 3 ft. column in petroleum ether (30°-40°). It was eluted with petroleum ether followed by graded mixtures up to 2:98 of diethyl ether/petroleum ether. Fractions were combined and evaporated to give 0.77 g (31 percent) of material which was identical in all respects to an authentic sample: $[\alpha]_D -176^\circ$ (CHCl₃), gas-liquid chromatographic purity >96 percent.

The above reaction was repeated on a larger scale using 28.8 g of olivetol, 24.5 g of (+)-*cis/trans*-*p*-mentha-2,8-dien-1-ol, 20 g of anhydrous magnesium sulfate and 1 L. of methylene chloride. To the cooled (0° C) well-stirred solution was added 10.0 mL of boron trifluoride etherate. The temperature was maintained at 0° C and stirring was continued for 1.5 hr. Fifty grams of anhydrous sodium carbonate was added and the workup was continued as described above. After evaporation of the solvent, there was obtained 54 g of light brown gum. Gas-chromatographic analysis of an aliquot revealed that the mixture contained 42 percent of (-)-6a,10a-*trans*-1-hydroxy-3-*n*-pentyl-6,6,9-trimethyl-6a,7,8,10a-tetrahydrodibenzo[b,d]pyran.

Example VII

A mixture of 153 mg (0.85 mmol) of olivetol, 132 mg (0.87 mmol) of (+)-*cis/trans*-*p*-mentha-2,8-dien-1-ol and 200 mg of anhydrous magnesium sulfate in 5 mL of methylene chloride was stirred and cooled to ice bath temperature. Fifty microliters of anhydrous stannic chloride (0.111 g, 0.4 mmol) was added and stirring and cooling was continued. After 10 minutes, the reaction mixture was analyzed by gas-liquid chromatography and shown to contain 30 percent of (-)-6a,10a-*trans*-1-hydroxy-3-*n*-pentyl-6,6,9-trimethyl-6a,7,8,10a-tetrahydrodibenzo[b,d]pyran. After quenching the reaction with sodium carbonate, the desired compound can be isolated from the reaction mixture.

Other References

Cardillo et al., *Gazz Chim. Ital.*, 103, 127 (1973).

Razdan et al., *JACS*, 96, 5860 (1974).

Source: Razdan 1978

Preparation of Optically Active *trans*-Hexahydrodibenzopyranones

by Robert A. Archer of Indianapolis, IN;

William A. Day of Indianapolis, IN

November 10, 1976

The preparation of 1-hydroxy-3-substituted-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-ones was first reported by Fahrenholtz, Lurie and Kierstead, *J. Am. Chem. Soc.*, 88, 2079(1966); 89,5934(1967). The reported synthesis provided predominantly the *dl*-6a,10a-*trans* compound, with minor quantities of the corresponding *dl*-6a,10a-*cis* isomer being isolated. The compounds were used by Fahrenholtz et al. only as intermediates, and no pharmacological activity was attributed to them. It recently has been discovered that such hexahydrodibenzopyranones have a variety of useful biological properties, and accordingly are valuable in the treatment of various mammalian disorders. *U.S. Pat.* Nos. 3,953,603, 3,944,673, and 3,928,598, describe the use of hexahydrodibenzopyranones in the treatment of anxiety, depression, and for imparting analgesia. Particular attention is drawn to *dl-trans*-1-hydroxy-3-(1,1-dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one, an especially potent drug generically referred to as Nabilone.

It now has been learned that certain *dl-trans*-hexahydrodibenzopyranones are more active pharmacologically than the corresponding *dl-cis*-isomers. Further resolution of such *dl-trans* racemates has led to the discovery that essentially all of the biological activity displayed by a *dl-trans*-hexahydrodibenzopyranone is possessed by the optically active isomers wherein the 6a and 10a hydrogen atoms both have the R absolute configuration. The optically active *trans* isomers wherein the 6a and 10a hydrogen atoms both have the S absolute configuration are particularly useful as intermediates in the synthesis of compounds having valuable central nervous system activity. It therefore becomes desirable to have a stereoselective synthesis of such optically active *trans*-hexahydrodibenzopyranones.

According to the process of this invention, optically active apoverbenone is reacted with a 5-substituted resorcinol. Examples of commonly used 5-substituted resorcinols are the 5-alkyl resorcinols such as 5-*n*-pentyl resorcinol, 5-(1,1-dimethylheptyl)resorcinol, 5-(1,2-dimethylheptyl)resorcinol, 5-(*n*-octyl)resorcinol, and the like. Either

(+)-apoverbenone or (-)-apoverbenone and a 5-substituted resorcinol generally are utilized in approximately equimolar quantities, although an excess of either reactant can be used if desired. The reaction is carried out in the presence of approximately an equimolar quantity of aluminum chloride, and is best conducted in the presence of an unreactive organic solvent. Typical solvents generally utilized include aromatic solvents such as benzene, chlorobenzene, toluene, and xylene, and halogenated hydrocarbons such as chloroform, dichloromethane, 1,2-dibromoethane, chloropropane, and related solvents. The reaction typically is carried out at a temperature from about -20°C . to about 50°C ., and preferably is conducted at a temperature from about -10°C . to about 30°C . When carried out at such temperature, the reaction normally is substantially complete within about 24 to 120 hours, although longer reaction times can be employed if desired. The reaction most typically is complete within about 48 to about 96 hours. The product of the process, an optically active *trans*-1-hydroxy-3-substituted-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-di benzo-[b,d]pyran-9-one, can be readily isolated by simply diluting the reaction mixture with water or ice, and then extracting the water-insoluble product therefrom into a suitable water immiscible organic solvent such as benzene, diethyl ether, chloroform, or the like. The organic layer can be washed with an aqueous acid and an aqueous base in the usual manner if desired, and the removal of the solvent therefrom provides the desired product. Such product can be further purified if desired by any of a number of routine procedures, including chromatography, crystallization, and the like.

As hereinabove noted, the process of this invention utilizes as starting materials 5-substituted resorcinols and (+) and (-)-apoverbenone, which can be prepared according to the method of Grimshaw et al., *J. Chem. Soc. Perkin I*, 50 (1972), in which readily available (+) and (-)- β -pinene is brominated to form a bromonopinone, which upon dehydrobromination affords an optically active apoverbenone. According to the process of this invention, reaction of a 5-substituted resorcinol with (+)-apoverbenone affords a *trans*-hexahydrodibenzo[b,d]pyran-9-one in which the 6a and 10a hydrogen atoms both have the R absolute configuration. Reaction of a 5-substituted resorcinol with (-)-apoverbenone affords a *trans*-hexahydrodibenzo[b,d]pyran-9-one in which the 6a and 10a hydrogen atoms both have the S absolute configuration.

1-hydroxy-3-(1,1-dimethylheptyl)-6,6-dimethyl-6,6aR,7,8,10,10aR-hexahydro-9H-dibenzo[b,d]pyran-9-one

A solution of 1.6 g. of (+)-apoverbenone in 50 ml. of dichloro-methane containing 2.8 g. of 5-(1,1-dimethylheptyl)resorcinol was cooled to 0° C. in an ice bath and stirred while 1.6 g. of aluminum chloride was added in one portion to the reaction mixture. The reaction mixture then was allowed to warm to about 25° C., and stirring was continued at that temperature for 72 hours. The reaction mixture was then poured into 50 g. of ice, and the aqueous mixture was extracted several times with diethyl ether. The ethereal extracts were combined, washed with 2N hydrochloric acid solution and then with water, and finally with five percent aqueous sodium bicarbonate solution. The organic layer was separated, dried, and the solvent was removed by evaporation under reduced pressure to provide 4.5 g. of the title compound as a crude oil. The oil so formed was chromatographed over a Woelm silica gel activity II column, eluting with benzene. Fractions shown by thin layer chromatography to contain the desired product were combined, and the solvent was removed therefrom to afford 720 mg. of 1-hydroxy-3-(1,1-dimethylheptyl)-6,6-dimethyl-6,6aR,7,8,10,10aR-hexahydro-9H-dibenzo[b,d]pyran-9-one.

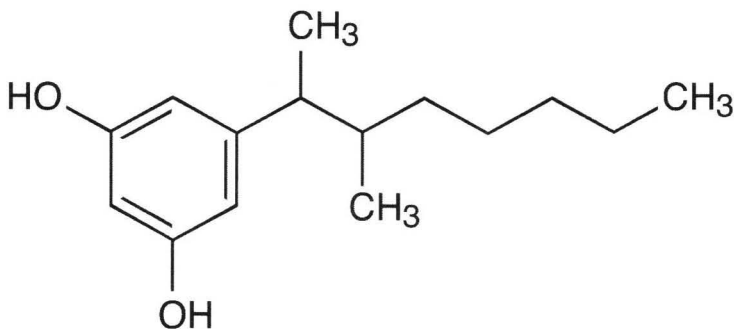
Other References:

Razdan et al., *J. Am. Chem. Soc.*, 92, 6061 (1970).

Mechoulam, *Marijuana*, pp. 48-50 (1973).

Grimshaw et al., *J. Chem. Soc., Perkin*, 50 (1972).

Source: Archer 1978



1,2-Dimethylheptylresorcinol

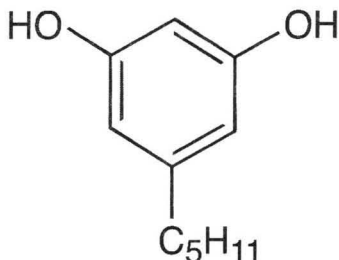
Producing 6a,10a-*Trans*-6a,7,8,10a-tetrahydrodibenzo (b,d)-pyrans

by Theodor Petrzilka

Erlenbach Switzerland

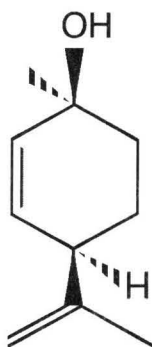
July 2, 1970

The compounds of formula II can be synthesized by condensing in the presence of an acid agent, a resorcinol of the formula:



Olivetol

or with (+) *p*-menthadien (2,8)-ol-(1) which has the general formula:



(+)-*trans*-*p*-Menthadien-(2,8)-ol-(1)

As examples of the compounds of formula IV above that can be utilized in the process of this invention are included resorcinol,

5-ethyl resorcinol, 2-(3,5-dihydroxyphenyl) hexane, 2-(3,5-dihydroxyphenyl)-3-methyl octane, 5-*n*-propyl resorcinol, 5-methyl resorcinol (orcinol), 5-*n*-pentyl resorcinol (olivetol), 5-(1-methylbutyl)-resorcinol, 5-*n*-hexylresorcinol, 5-(1-ethylbutyl)-resorcinol, 5-(1,1-dimethyl-butyl)resorcinol, 5-(1,2-dimethylbutyl)-resorcinol, 5-*n*-heptylresorcinol, 5-(1-methylhexyl) -resorcinol, 5-*n*-octylresorcinol, 5-(1-*n*-propylpentyl) -resorcinol, 5-(1-methyloctyl)-resorcinol and the like.

Any of the isomers of (+)-*p*-methadienol-(1) of formula VI above which are (+)-*cis* and (+)-*trans*-*p*-menthadienol-(1) as well as the racemic mixture thereof can be utilized in the process of this invention to produce the compound of formula I above.

The condensation of compounds of the formula IV with compounds of the formulas V or VI can be carried out in a conventional inert solvent. Among the preferred solvents are included aliphatic or aromatic hydrocarbons such as petroleum ether, benzene, toluene, etc.;

halogenated aliphatic or aromatic hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride, chlorobenzene, etc.; nitrated hydrocarbons such as nitrobenzene, etc.; and ethers such as diethyl ether, tetrahydrofuran, dioxan, etc. Among the other conventional solvents which are preferred to be utilized in the process of this invention are included dimethylformamide, dimethylsulphoxide, or liquid sulphur dioxide.

The reaction to produce the compound of formula II above is carried out in the presence of any conventional organic or inorganic acid agents. Among the preferred acid agents which can be utilized in carrying out the process of this invention are included Lewis acids such as boron trifluoride, zinc chloride, aluminum chloride, tin tetrachloride, etc.; mineral acids such as hydrochloric acid, hydrobromic acid, hydrofluoric acid, sulfuric acid, phosphoric acid, polyphosphoric acids, etc.; and organic acids such as *p*-toluene sulphonic acid, methane sulphonic acid, formic acid, glacial acetic acid, trifluoroacetic acid, trichloroacetic acid, oxalic acid, maleic acid etc. Sulphur dioxide can be utilized as both the acid medium and the organic solvent. Therefore, when liquid sulphur dioxide is utilized as the solvent medium, the reaction of this invention will take place without the addition of any other acid agent.

In carrying out the reaction to produce the compound of formula II above, temperature and pressure are not critical and this reaction can be carried out at room temperature and atmospheric pressure. If desired, lower or elevated temperatures can be utilized. This condensation reaction is advantageously effected at a temperature of from about 0° C. to about 120° C. In a preferred embodiment of this invention, the reaction is particularly preferably carried out in the presence of *p*-toluene-sulphonic acid in benzene by heating to a temperature of about 80° C. for 2 hours under reflux conditions.

The compounds of formula III above are prepared from the compound of formula II above by treating the compound of formula II above with a hydrohalic acid in the presence of a metal halide. In this reaction, the halide group of the metal halide should be the same as the halide group of the acid halide. The metal halide can be formed from any Group II metal, Group III and Group IV metal of the periodic chart. Among the metal halides which can be utilized are included aluminum bromide, aluminum chloride, stannic chloride, boron trifluoride, magnesium chloride, titanium chloride, ferric chloride, etc. The preferred metal halide utilized in accordance with this invention is zinc chloride. Any conventional hydrohalic acid such as hydrochloric, hydrobromic, etc can be utilized. Generally, this reaction is carried out in the presence of an inert organic solvent. Any conventional inert organic solvent can be

utilized. The preferred solvents are the halogenated hydrocarbon solvents such as methylene chloride. In carrying out this reaction, temperature and pressure are not critical, and this reaction can be carried out at room temperature and atmospheric pressure. If desired, elevated or lower temperatures can be utilized.

In accordance with a preferred embodiment of this invention, the compound of the formula II above is converted to a compound of the formula III above by treating the compound of the formula II above with zinc chloride in a methylene chloride solution saturated with hydrogen chloride.

The following examples are illustrative but not limitative of this invention. All temperatures are in degrees centigrade. The ether utilized in the examples is diethyl ether. The pressure utilized in the examples is expressed as mmHg.

A solution of 360 mg. of olivetol and 270 mg. of (+)-*p*-menthatriene-(1,5,8) in 7 mL. of liquid sulphur dioxide is allowed to stand at room temperature for 24 hours in a sealed tube. The sulphur dioxide is thereupon evaporated off under a calcium chloride tube. The oily residue is dissolved in diethyl ether. The ether solution is extracted once with dilute sodium hydrogen carbonate and dried over sodium sulphate. After evaporation of the ether, 633 mg. of a yellow resin remains. The yellow resin which is obtained, is chromatographed on 20 g. of silica gel and upon elution with benzene and distillation at high vacuum, 168 mg. of (+)-1-hydroxy-3-*n*-amyl-6,6,9-trimethyl-6a,10a-*trans*-6a,7,10,10a-tetrahydrodibenzo(b,d)pyran is obtained. The RF value of the tetrahydrodibenzopyran obtained is 0.46; boiling point 140°-150° C/0.001 mmHg. (silica gel thin layer chromatogram in chloroform).

Example 2

A mixture of 450 mg. of olivetol, 380 mg. (+)-*cis*-*p*-menthadiene-(2,8)-ol-(1) and 58 mg. of *p*-toluenesulphonic acid monohydrate in 25 mL. of benzene is boiled under reflux for 2 hours. The resulting orange-yellow solution is cooled in an ice-water bath and dissolved in diethyl ether. The ether solution is immediately shaken once with dilute sodium hydrogen carbonate solution and once with sodium chloride solution. The almost completely decolorized ether solution is dried over sodium sulphate. After evaporation of the ether, 818 mg. of a light yellow oil remained. The resulting yellow oil is chromatographed on 35 g. of silica gel and upon elution with benzene and distillation at high vacuum, 384 mg. of (-)-1-hydroxy-3-*n*-amyl-6,6,9-trimethyl-6a,10a-*trans*-6a,7,10,10a-tetrahydrodibenzo(b,d)-pyran is obtained.

Example 7

A solution of 0.427 g. (2.37 mMol) of olivetol and 0.356 g. (2.34 mMol) of (+)-*trans-p*-menthadien-(2,8)-ol-(1) in liquid sulphur dioxide is allowed to stand at room temperature for 70 hours in a sealed tube. Thereafter, the solvent medium is carefully distilled off. The residue is dissolved in 50 mL. of diethylether. The ether solution is extracted once with a dilute sodium bicarbonate solution. After extraction, the ether solution is dried and evaporated. The dry residue (0.74 g.), which is obtained is chromatographed on silica gel and eluted.

One obtains after distillation utilizing a high vacuum, 142 mg. of (-)-1-hydroxy-3-*n*-amyl-6,6,9-trimethyl-6a,10a-*trans*-6a,7,10,10a-tetrahydrodibenzo(b,d)-pyran. This compound has an RF value (silica gel thin layer chromatogram in chloroform) of 0.51 and a boiling point of 140°-150°C./0.001 mmHg.

Example 8

0.595 g. (3.3 mMol) olivetol is mixed with 0.502 g. (3.3 mMol) (+)-*cis-p*-menthadien-(2,8)-ol-(1) in 8 mL. of liquid sulphur dioxide. This mixture is allowed to stand at room temperature for 120 hours in a sealed tube. After working up the mixture in the manner described in Example 1, 1.085 g. of an oily residue is obtained. The oil is chromatographed over silica gel and eluted. Upon distillation in high vacuum, 215 mg. of (-)-1-hydroxy-3-*n*-amyl-6,6,9-trimethyl-6a,10a-*trans*-6a,7,10,10a-tetrahydrodibenzo(b,d)-pyran is obtained. This compound has an RF value (silica gel thin layer chromatogram in chloroform) of 0.52 and a boiling point of 140°-150° C./0.001 mmHg.

Example 9

A mixture of 0.54 g. (3 mMol) of olivetol, 0.46 g. (3 mMol) of (+)-*trans-p*-menthadien-(2,8)-ol-(1) and 0.5 mL. of trifluoro acetic acid in 50 mL. of benzene is refluxed for 5 hours. The resulting solution is worked up in the manner of Example 2 to yield 0.95 g. of a residue. The resulting residue is chromatographed on silica gel and upon elution and distillation at high vacuum yields 520 mg. of (-)-1-hydroxy-3-*n*-amyl-6,6,9-trimethyl-6a,10a-*trans*-6a,7,10,10a-tetrahydrodibenzo(b,d)9pyran. This compound has an RF value (silica gel thin layer chromatogram in chloroform) of 0.52 and a boiling point of 140°-150°C./0.001 mmHg.

Example 10

A mixture of 2.2 g. (20 mMol) of crystalline resorcinol, 3.05 g. (20 mMol) (+)-*trans*-*p*-menthadien-(2,8)-ol-(1) and 0.4 g. (2 mMol) of *p*-toluene sulphonic acid monohydrate in 50 mL. of benzene is heated under reflux for 2 hours. The resulting solution is dissolved in 50 mL. of diethyl ether. The ether is extracted once with dilute sodium bicarbonate solution. The ether phase is dried and evaporated. 5.1 g. of a yellow oil is obtained. This oil is chromatographed on 250 g. of silica gel and eluded with benzene. After distilling off the benzene under high vacuum, there is obtained 778 mg. of (-)-1-hydroxy-6,6,9-trimethyl-6a,10a-*trans*-6a,7,10,10a-tetrahydrodibenzo(b,d)-pyran. This compound has an RF value (silica gel thin layer chromatogram in chloroform) of 0.35 and a boiling point of 155°C./0.001 mmHg.

Other Publications

Gaoni et al., *J. Am. Chem. Soc.*, Vol. 86, pp. 1646- 1647 (1964)

Source: Petrzilka 1972

Dibenzo[b,d]pyrans and Process

by Edward C. Taylor and Katherine Lenard
Princeton, New Jersey January 11. 1966

The inventive process comprises the acid-catalyzed condensation of citral (II) with a resorcinol (III).

This process makes available either the Delta 8,9 or the Delta 9,10 compounds, depending upon the conditions used, the principal controlling variable being the strength of the acid catalyst. When a strong acid is used as the catalyst, the product is a mixture of the *cis* and *trans* isomers of the Delta-8,9 compounds. These isomers are separable by vapor phase chromatography. Among the operative strong acids are mineral acids such as conc. sulfuric acid and conc. hydrochloric acid, and Lewis acids such as boron trifluoride, preferably in the form of the etherate, aluminum chloride, and ferric chloride. When a mild acid is used, the product consists of a mixture of the *cis* and *trans* isomers of the Delta 8,9 compounds. Among the operative mild acids are dilute hydrochloric, dilute acetic acid, and dilute sulfuric acid.

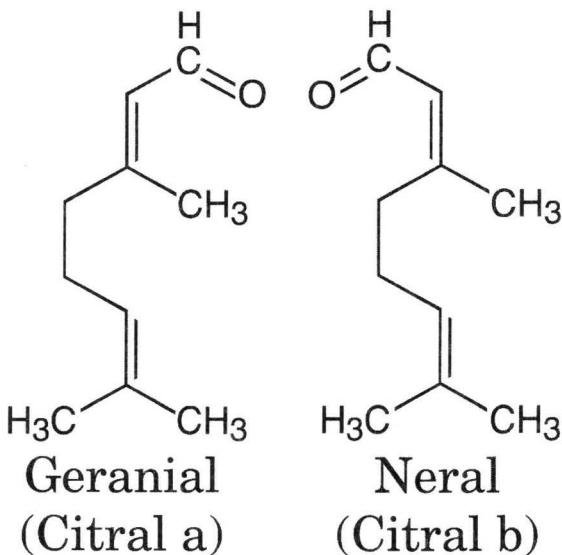
The condensation is conducted in polar organic solvents such as ethanol and isopropanol, or in nonpolar solvents such as benzene, toluene, xylene, and ethyl acetate.

However, choice of solvent is not a critical factor in carrying out the reaction.

The process can be conducted within a temperature range of about 0 to 110°, the consequence of using temperatures higher than room temperature being to cause exclusive formation of the Delta 8,9 isomers, regardless of the strength of the acid catalyst employed. Higher temperatures thus override the otherwise controlling effect of acid strength. At temperatures near or below room temperature, the product is either the Delta 8,9 or Delta 9,10 isomer, the nature of the product being controlled by the strength of the acid catalyst. A temperature range of 0-30° when employed in conjunction with a mild acid catalyst insures the formation of the Delta 9,10 isomer. The range 5-10° is most preferred.

The time of the reaction is not critical, 1 to 24 hours being a suitable time.

Commercial citral is a mixture of two geometric isomers. Geranial is the *cis* compound, i.e., the isomer in which the formyl and methyl groups bear a *cis* relationship to each other; neral is the *trans* compound. Either isomer or a mixture thereof, as in citral, is suitable as a reactant in the present process. The term "citral" as used herein is thus intended to signify a mixture of the *cis* and *trans* isomers, although either isomer may be used as a starting material.



The resorcinols used as starting materials in the present process are either resorcinol itself (III, R=H) or a 5-alkylresorcinol (III, R=alkyl). The alkyl group may have up to twelve carbon atoms and it may be either branched or straight-chained. Examples of such alkyl groups are methyl, ethyl, propyl, sec-butyl, pentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1-ethyl-2-methylpropyl, isohexyl, heptyl, 1-methylhexyl, 1,2-dimethylhexyl, 1,2-dimethylheptyl, 1-methyloctyl, and 1-methylnonyl.

The inventive process is practiced in the following manner, being illustrated for the preparation of a Delta 8,9 isomer: Citral, a resorcinol, and an acid catalyst such as boron trifluoride-etherate in a solvent such as benzene are stirred with cooling for a period of thirty minutes to about two hours. To insure complete reaction, the reaction mixture is then allowed to stand for a period of several hours, conveniently overnight. The reaction mixture is then worked up by conventional procedures, preferably by addition of water and extraction with an organic solvent such as ether. The crude product is then chromatographed in order to obtain a mixture of the *cis* and *trans* products. The *cis* and *trans* isomers are separable using vapor phase chromatography.

3-(1,2-Dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6,9-trimethyl-6H-dibenzo[b,d]pyran

To a mixture of 9.4 g. (40 mmoles) of 5-(1,2-dimethylheptyl)-resorcinol and 7.0 g. (46 mmoles) of commercial citral in 50 mL. of benzene is added, with stirring and cooling over a 30 minute period, 7.0 g. of boron trifluoride etherate diluted with 15 mL. of benzene. The reaction mixture is stirred for an additional hour and is then allowed to stand at room temperature overnight. It is then diluted with 100 mL. of water and extracted with ether, the ether extracts washed with water, 2 N sodium hydroxide and again with water, dried over anhydrous magnesium sulfate and evaporated. The residual resinous oil (14.2 g.) is then chromatographed on 350 g. of Florisil. Elution of the column With hexane gives a small amount (1.05 g.) of a nonphenolic compound which is discarded. Subsequent elution with hexane-ethyl ether (95.5) then gives a mixture of racemic *cis* and racemic *trans*-3-(1,2-dimethylheptyl)6a,7,10,10a-tetrahydro-1-hydroxy-6,6,9-trimethyl-6-dibenzo[b,d]pyran, separated by vapor phase chromatography (instrument, F and M model 810; column, 3/4" x 6' copper, 6% GE-SE 30 on Diatoport S, 100-200 mesh; column temp., 245°; gas, helium; flow rate, 75 mL./min.; inlet temp., 390°; detector temp., 370°; injection, 20 micro-liters of a 50% hexane solution). Source: Taylor 1968

Chapter 6: 5-Alkylresorcinols

Preparation of 1-Hydroxy-2,6-dimethoxy-4-(tertiary alkyl)benzene

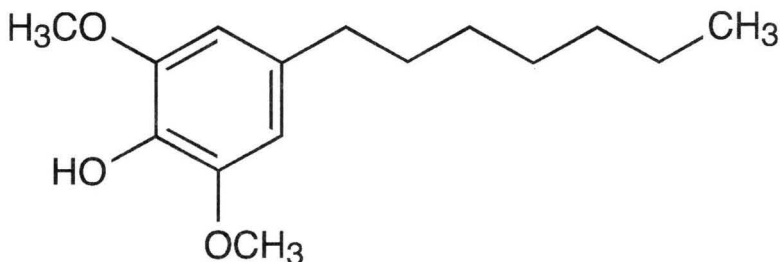
by Samuel J. Dominianni and Charles W. Ryan
Indianapolis, Ind. June 14, 1976

It has now been discovered that 2,6-dimethoxyphenol surprisingly is alkylated almost exclusively at the 4-position by reaction with a tertiary carbinol in the presence of an acid. Such alkylation provides a 1-hydroxy-2,6-dimethoxy-4-(tertiary alkyl)benzene which can readily be converted to a 5-(tertiary alkyl)resorcinol. Such process affords high yields of the desired 5-(tertiary alkyl)resorcinol... starting from relatively inexpensive starting materials.

The reaction between the 2,6-dimethoxyphenol and the tertiary carbinol is carried out in the presence of an acid such as a sulfonic acid, for example methanesulfonic acid, sulfuric acid, *para*-toluenesulfonic acid and the like. An especially preferred acid is methanesulfonic acid. The alkylation reaction generally is carried out by commingling approximately equimolar quantities of the 2,6-dimethoxyphenol and the tertiary carbinol in the presence of an acid. The amount of acid utilized is not critical, and if desired, excessive amounts of acid can be utilized to the extent that such acid acts as solvent for the reaction in addition to being an alkylation catalyst. Alternatively the reaction can be carried out in a solvent such as dioxane, tetrahydrofuran, dimethyl sulfoxide, and the like, with about one molar quantity of acid being employed as catalyst. The reaction can be carried out at any temperature ranging from about 25° to about 80° C., and normally is conducted at about 50. C. The alkylation is usually substantially complete within about 1 to about 10 hours; however, longer reaction times can be used if desired. The product typically is isolated by simply removing the acid from the reaction mixture, for instance by adding the reaction mixture to a water immiscible solvent such as dichloromethane or ethyl acetate, and washing the solution several times with water, and if desired with an aqueous base such as a sodium bicarbonate solution in order to effect complete removal of any residual acid. Removal of the solvent from the organic solution then provides the product, which typically needs no further purification. While it would be expected that the position of

alkylation of 2,6-dimethoxyphenol would be governed by the *ortho-para* directing influences of the two methoxy groups, the above-described alkylation process surprisingly effects substantially predominantly substitution at the position meta to the two methoxy groups, thus providing almost exclusively a 1-hydroxy-2,6-dimethoxy-4-(tertiary alkyl)benzene. Such result is indeed surprising and represents a significant advance in the technology of producing 2,6-dimethoxy-4-(tertiary alkyl)phenols. A known process for preparing such compounds is that described in *U.S. Pat. No. 2,888,503*, which process comprises reacting 2,6-dimethoxyphenol with an alkenyl bromide to provide a 1-alkenoxy-2,6-dimethoxybenzene, which compound is then rearranged, generally by heating, to provide a 1-hydroxy-2,6-dimethoxy-4-alkenylbenzene.

1-Hydroxy-2,6-dimethoxy-4-(1,1-dimethylheptyl)benzene



1-Hydroxy-2,6-dimethoxy-4-(heptyl)benzene

A solution containing 15.4 g. of 1-hydroxy-2,6-dimethoxybenzene and 14.4 g. of 1,1-dimethyl-1-hydroxyheptane in 20 mL. of methane-sulfonic acid was heated at 50° C. and stirred for three and one-half hours. The reaction mixture next was poured over 50 g. of ice, and the resulting aqueous solution was extracted several times with dichloromethane. The organic extracts were combined, washed with water and with saturated aqueous sodium bicarbonate solution, and dried. Removal of the solvent by evaporation under reduced pressure provided 27.4 g. of 1-hydroxy-2,6-dimethoxy-4-(1,1-dimethylheptyl)benzene as an oil. Source Dominianni 1978

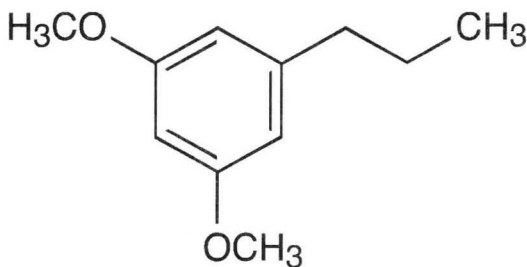
A mixture of 2,6-dimethoxyphenol (73.4 g., 0.48 mole), 2,6-dimethyl-2-heptanol (69.0 g., 0.48 mole) and methane-sulfonic acid (95 mL.) was stirred at 50° C. for 3 hours and then at room temperature overnight.

The mixture was poured over ice-water (600 mL.) with stirring. The mixture was extracted with CH_2Cl_2 (2x200 mL.). The extracts were washed with water, saturated aqueous NaHCO_3 , saturated aqueous sodium chloride solution and dried over anhydrous Na_2SO_4 . The solution was concentrated under reduced pressure to obtain the product as an oil (130) g., 96%). Source: Travis 2001

See also: **Dominianni et al.**, *J. Org. Chem.*, 42, 344-46 (1977); **Baek et al.**, *Arch. Pharm. Res.*, 19, 228-30 (1996); **Guthrie et al.**, *J. Org. Chem.*, 47, 2369-76 (1982)

Divarin Dimethyl Ether from 3,4,5-Trimethoxy-propiophenone

by Yasuhiko Asahina Tokyo, Japan May 20, 1936
Translated by Otto Snow



Divarin Dimethyl Ether

A solution of 15 g 3,4,5-trimethoxy propiophenone in a little absolute alcohol is stirred in, under warming in a bath (of saturated chlorine calcium solution), alternating with larger pieces sodium and alcohol, whereby at least 75 g sodium and 600 ccm absolute alcohol is necessary. After the sodium disappears in the mixture, is diluted with water (2L), acidified with hydrochloric acid, the alcohol distilled and then extracted with ether. Evaporation of the ether leaves 9 g of Divarin dimethylether. Source: Asahina 1936 For use of selenium dioxide to crack off para methoxy group see page 180 in *Amphetamine Syntheses Industrial*.

Reduction of Ketones to Resorcinols

Synthesis of 5-Alkylresorcinols

by Yasutaka Miura, of Takatsuki; Yasuhiro Kinoshita and Yoshikazu Yamamoto both of Neyagawa; Kunio Takahashi of Urawa; Kiyotaka Koyama and Kaoru Takatori of Higashikurume all of Japan

Synthesis of 5-Ethylresorcinol

The reduction was conducted by adding water (300cc), concentrated hydrochloric acid (300 cc) and 3,5-dihydroxyethylphenone (100 g) to zinc amalgam obtained from zinc (400 g) and mercuric chloride (20 g). Further, concentrated hydrochloric acid (10 to 15 cc) was added every one hour. After the completion of the reaction, the reaction solution was cooled and saturated with sodium chloride, and then extracted with ether to obtain 88 g of 5-ethylresorcinol. Reference: Roufogalis 1999

Preparation of Hexylresorcinol by Electrolytic Reduction of Hexanoylresorcinol

Catholyte in unglazed porcelain cylinder containing 100 mL. 35% H₂SO₄ and 10g. hexanoylresorcinol.

Cathode: Zn-Hg cathode

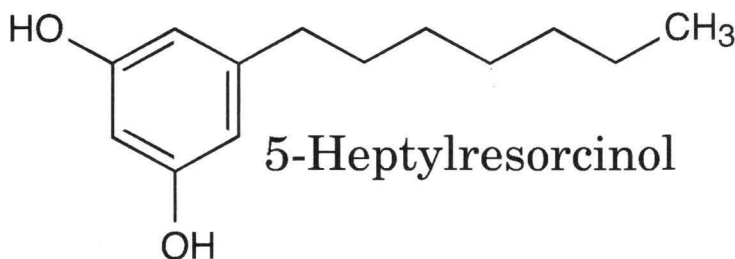
Anode: Lead container

Anolyte: 35% sulfuric acid

Electrolyzed with a current density of 12 amp./sq. dm. at 3 v.

Temperature: 80°

The product floats to the top as an oil. Distillation of oil produces a yield of 71% hexylresorcinol. Reference: Hirayama 1951



See *Amphetamine Syntheses Industrial* for a detailed description of the electrolytic reduction apparatus.

Synthesis of 5-Methylresorcinol (Orcinol)

Methylmagnesium bromide (35 g) was added to 1,3-dimethoxy-5-benzoyl chloride (100 g) to obtain 1,3-dimethoxy-methylphenone in a yield of 45%. Then, the reduction was conducted by adding water (300 cc), concentrated hydrochloric acid (300 cc) and 1,3-dimethoxy-methylphenone (100 g) to zinc amalgam obtained from zinc (400 g) and mercuric chloride (20 g). Further, concentrated hydrochloric acid (10 to 15 cc) was added every one hour. After the completion of the reaction, the reaction solution was cooled and saturated with sodium chloride, and then extracted with ether to obtain 40 g of 1,3-dimethoxy-5-methylbenzene. Hydrogen iodide was added to the resulting 1,3-dimethoxy-5-methylbenzene and stirred at 115° to 125° C. for 3 hours under nitrogen atmosphere. After cooling, the product was extracted with methylene chloride to obtain 30 g of 5-methylresorcinol.

Source: Miura 1995



5-Alkylresorcinol from Demethylation of 1-(Alkyl)-3,5-Dimethoxybenzene

The next step in the instant process involves cleavage of the two methyl ether groups of the 1-(tertiary alkyl)-3,5-dimethoxybenzene by reaction with a demethylating agent to provide the corresponding 5-(tertiary alkyl)-resorcinol. Such cleavage can be accomplished by simply heating the dimethoxy derivative in a mixture of pyridine hydrochloride. Such mixture is heated at reflux for a period of time ranging from about 2 to 10 hours, thus effecting cleavage of the two methyl ether groups. Alternatively, the 1-(tertiary alkyl)-3,5-dimethoxybenzene can be reacted with a boron trihalide such as boron tribromide or boron trichloride, or an aluminum halide such as aluminum bromide or aluminum chloride, thus effecting cleavage of the two methyl ether groups. Such reaction typically is carried out in a solvent such as dichloromethane or n-pentane, and generally is conducted at a reduced temperature ranging from about -80° to 25° C. The product, a 5-(tertiary alkyl)resorcinol, is isolated by evaporation of the solvent, and further purification can be

accomplished by crystallization or chromatography. Cleavage of the two methyl ether groups can additionally be effected by reaction of the 1-(tertiary alkyl)-3,5-dimethoxybenzene with a mixture of hydrobromic acid in acetic acid.

As hereinbefore pointed out, the 5-(tertiary alkyl)resorcinols thus prepared in accordance with this invention are important intermediates in the preparation of useful drugs. For example, 5-(1,1-dimethylheptyl)resorcinol is utilized in the preparation of 1-hydroxy-3-(1,1-dimethylheptyl)-6,6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9H-dibenzo[b,d]pyran-9-one, which compound is extremely useful in the treatment of depression in humans, as described in *U.S. Pat. Nos.* 3,928,598, 3,944,673, and 3,953,603. Similarly, 5-(1,1-dimethylheptyl)resorcinol is required in the synthesis of 3-(1,1-dimethylheptyl)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-6H-dibenzo[b,d]pyran-1,9-diol, which compound is useful as a blood-pressure lowering agent. It can thus be seen that a commercially feasible process for preparing 5-(tertiary alkyl)resorcinols in high yield is desirable.

Demethylation Using Pyridine 5-(1,1-Dimethylheptyl)resorcinol

A mixture of 21.2 g. of 1-(1,1-dimethylheptyl)-3,5-dimethoxybenzene and 55 g. of pyridine hydrochloride was heated at reflux and stirred for 5 1/2 hours. The reaction mixture then was cooled to room temperature and added to 150 mL. of water. The aqueous solution was extracted several times with diethyl ether, and the ethereal extracts were washed with water and dried. Removal of the solvent by evaporation under reduced pressure provided the product as a solid residue. The solid was recrystallized from 40 mL. of n-hexane to afford 13.0 g. of 5-(1,1-dimethylheptyl)resorcinol. M.P. 97°-99° C.

Demethylation Using 48% Hydrobromic Acid 5-(1,1-dimethylheptyl)resorcinol

A solution of 425 g. of 1-(1,1-dimethylheptyl)-3,5-dimethoxybenzene in 1700 mL. of glacial acetic acid containing 850 mL. of 48 percent aqueous hydrobromic acid was stirred and heated at reflux for 12 hours. The reaction mixture was cooled to room temperature and added to 6000 mL. of water. The aqueous reaction mixture was stirred while the product crystallized out of solution. Filtration of the mixture afforded 371 g. of 5-(1,1-dimethylheptyl)resorcinol. M.P. 93°-95° C.

Following the procedures set forth in Examples 4, 5 and 6, the respective 1-substituted-3,5-dimethoxybenzene was converted to the following resorcinol derivatives:

5-(1,1-Dimethylbenzyl)resorcinol M.P. 108°-110° C.

5-(1,1-Dimethylcyclohexylmethyl)resorcinol M.P. 145°-147° C.

5-(1-Methyl-1-n-hexylphenyl)resorcinol oil.

5-(1,1-Dimethyladamantylmethyl)resorcinol M.P. 125°-127° C.

5-Adamantylresorcinol M.P. 284°-285° C.

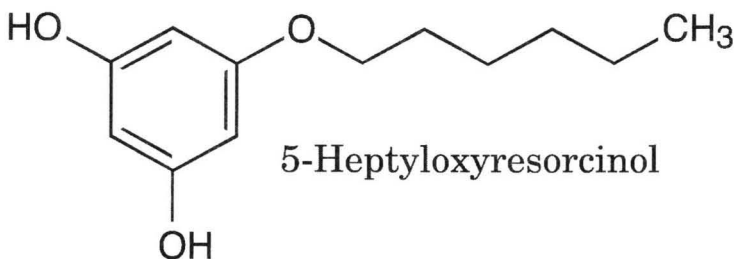
Source: Dominianni 1978 Reference: Dominianni 1978a; Winn 1979

Preparation of 5-Alkoxyresorcinols

by Bernard Loev of Broomall, Pa. July 18, 1973

To a stirred solution of 126 g. (1.0 mol.) of phloroglucinol and 19.0 g. (0.34 mol.) of potassium hydroxide in dimethylformamide was added 186 g. (1.04 mol.) of 2-bromoheptane. After heating the mixture for 16 hours at 100°, 250 mL. of acetic acid was added and the mixture was filtered. The filtrate was concentrated dissolved in ether, washed with water and extracted with 10% aqueous sodium hydroxide. The alkaline solution was washed with ether, acidified with dilute hydrochloric acid and extracted with ether. The organic phase was dried (MgSO₄), treated with charcoal and filtered. The solvent was evaporated and the residue was distilled to give 5-(1-methylhexyloxy)resorcinol as a resin, b.p. 165°-170° (0.15 mm.). Source: Loev 1974

5-(1-Methylhexyloxy)resorcinol is used in the preparation of 1-hydroxy-7,8,9,10-tetrahydro-3-(1-methylhexyloxy)-6,6,9-trimethyl-6H-dibenzo[b,d]pyran



Preparation of Phloroglucinol and its Mono-ethers

by Andreas J. J. Hendrickx and Nicolaas A. de Haij,
Venlo, Netherlands

June 23, 1972

The present invention is based on the discovery that resorcinol and resorcinol mono ethers, especially the mono-methyl ether, carrying a leaving group or substituent, such as a halogen atom, in the 4-, 5- or 6-position, will form a 4,5 or 5,6-yne bond, i.e. a triple carbon to carbon bond, when heated (or fused) in the presence of a proton abstracting agent, e.g. a strong alkali, whereupon water will react with the -yne bond product and result in the formation of phloroglucinol or its mono ether.

Instead of the dihydroxy benzene compounds or derivatives thereof mentioned above. monohydroxy benzene compounds also can be converted to phloroglucinol in like manner. The monohydroxy benzene compound however must carry two leaving groups at the right places so they can form two -yne bonds respectively between the C-atoms in the 3- and 5-positions. i.e. meta relative to the hydroxy group, and adjacent C-atoms of the benzene ring. 2,6-dichloro phenol is an example of a suitable monohydroxy compound.

While as a practical matter phloroglucinol is formed from 2,6-dichloro phenol in one reaction step, it can be supposed that 4-chloro resorcinol arises as an intermediate and is converted into phloroglucinol under the reaction conditions. Thus 2,6-dichloro phenol might be considered as a precursor to 4-chloro resorcinol under these conditions. For practical reasons, however, we consider these compounds to be equivalents and consider as precursors-all other compounds which upon reaction result in one of these two compounds.

The phenolic compounds reacted according to the invention thus are mono- or di-hydroxy benzene compounds having in the 3-position relative to a hydroxy group on the benzene ring a hydrogen atom, another hydroxy group, an alkyl, ether group, or a leaving group (substituent) that will depart from the compound upon reaction of it with a proton abstracting agent. Further, when the 3-position is occupied otherwise than by a hydrogen atom, such as leaving substituent is present in the 4-, 5- or 6-position; and when the 3-position is occupied by a hydrogen atom, two such leaving substituents are so positioned that two triple bonds can form respectively between the C-atoms at the

3- and 5-positions and carbon atoms adjacent thereto in the ring. Thus, in the latter case, one -yne bond can be formed between the carbon atoms at the 2- and 3- positions or the 3- and 4-positions and another -yne bond can be formed between the carbon atoms at the 4- and 5-positions or the 5- and 6-positions. Of course, the combination of two adjacent -yne bonds between the carbon atoms at the 3-, 4- and 5-positions does not occur, as this is chemically impossible.

Phenolic compounds of this nature which can be used advantageously are those which have a hydroxy group or said ether group in the 3-position and have a leaving substituent in the 4-position. Particularly useful compounds among these have at the 3-position a hydroxy group or an alkoxy group containing 1 to 4 carbon atoms, which desirably is a methylether group. Also advantageous are the mono-hydroxy benzene compounds which have leaving substituents in the two ring positions ortho to the hydroxy group, i.e., in the 2 and 6- positions.

The proton abstracting agent must be sufficiently strong to promote the formation of the -yne bond; so the hydroxides of the alkali metals lithium, sodium and potassium are of first choice. It reacts effectively at a molar ratio to the phenolic compound in the range between 12:1 and 30:1; a molar ratio of between 17:1 and 23:1 appears to be most advantageous.

The heating or fusion is preferably carried out in the presence of a very small amount of water, which may be, for example, about 1-10 mL. of water, preferably about 2 1/2 to 5 mL. thereof, per 100 g of alkali calculated as KOH.

The heating could be effected at temperatures as high as 300° C, which would be favorable with regard to reaction velocity, but it is preferred to apply relatively moderate temperatures, i.e. temperatures between 110° and 180° C, because aromatic polyhydroxy compounds are readily oxidized in alkaline media at temperatures above 180° C. Preferably the temperature is between 130° and 160° C.

Phloroglucinol is readily produced, and with overall yields of 50-70%, when starting with 4-chloro resorcinol, which is commercially available. To prepare the mono methyl ether, 4-chloro-3-methoxy phenol can be used. Of course the chlorine atom may also be in one of the two other suitable positions, i.e. the 5- or 6-position, and instead of chlorine in the starting material one of the other halogens may be employed. Useful starting materials thus include 4-chloro resorcinol, 5-chloro resorcinol, 4-bromo resorcinol, 5-bromo resorcinol, 4-chloro-3-methoxy phenol, 5-chloro-3-methoxy phenol, 6-chloro-3-methoxy phenol, 4-bromo-3-methoxy phenol, 5-bromo-3-methoxy phenol, and 6-bromo-3-methoxy

phenol. As the starting material those compounds are preferred in which a chlorine atom is present in the position ortho to a hydroxyl group.

In another advantageous practice of the invention, phloroglucinol is prepared by heating 2,6-dichloro phenol in the presence of a strong alkali and water. Instead of the 2,6-dichloro compound, the corresponding phenols having other halogen atoms in the 2 and 6 positions can be used, and likewise the halogen atom may be present in other suitable positions such as 2,4 or 2,5 or 3,5. Generally, every compound that upon reaction results in one of the starting materials mentioned above can be used as a precursor.

The following examples, which are not intended to be limiting further illustrate the practice of the invention.

EXAMPLE 1

40 g KOH (pellets) and 1.5 mL. of water were heated to 130° C. During 30 minutes, 5.5 g of 4-chloro-1,3-dihydroxybenzene (=4-chloro resorcinol) was added to the melt under vigorous stirring. The stirring was continued during 4 hours at 130° C. and then 50 mL. of water was added. The mixture was acidified with 59.5 mL. of HCl (s.g. 1.15) and extracted with ethyl acetate. After recrystallization from water phloroglucinol was obtained in 66% yield. It is not essential that water be added to the above mixture for reaction, but it appeared that by using 1-5 mLs of added water better results are obtained; the reaction mixture is easier to control yet the overall yield remains high.

EXAMPLE IV

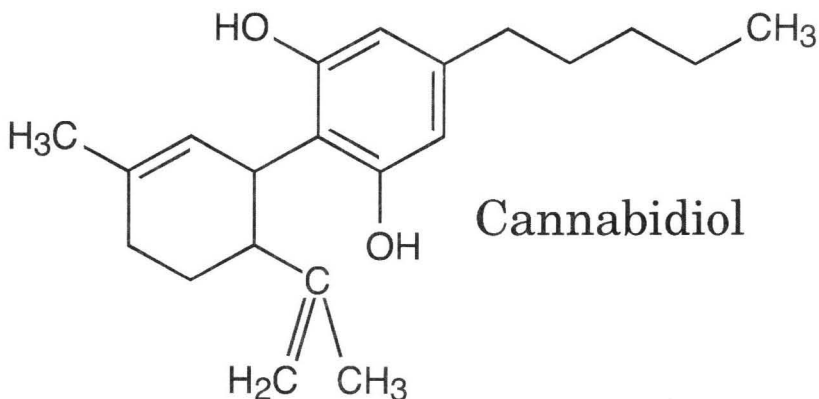
40 g KOH (pellets) and 1-2 mL. of water were heated to 150° C. To the melt 5 g of 2,6-dichloro phenol was added under stirring during approximately 30 minutes. The temperature was raised to 165°-175° C at which temperature the stirring was continued during two hours. Then the reaction mixture was cooled to 100° C. After addition of 50 mL. of water the mixture was acidified with 55-60 mL. of HCl (s.g. 1.15). Upon extraction with ethyl acetate and further refining, phloroglucinol in a 46% overall yield was obtained. On a second run according to this example the overall yield 49.1%.

Source: Hendrickx 1975

Chapter 7: Isomerisation Preparation of Compounds with Marijuana Activity from Cannabidiol

by Roger Adams Urbana, Illinois April 29, 1942

It has now been found that cannabidiol isomerizes upon treatment, for example, with a variety of reagents such as *p*-toluenesulfonic acid, sulfuric acid, hydrochloric acid and ethanol, hydrogen chloride in ether, pyridine hydrochloride, sulfamic acid, zinc chloride, ethanolic phosphoric acid, etc. and is converted to tetrahydro cannabinol which has marihuana activity and which may be represented by the following formula, with doubt merely in regard to the position of the double bond in the left-hand cycle.



Depending upon the exact conditions of the isomerization of the cannabidiol to tetrahydrocannabinol, the compositions or products formed may have rotations varying from approximately $130^{\circ}+5^{\circ}$ to $265^{\circ}+5^{\circ}$. A careful study has indicated that isomerizing reagents such as *p*-toluenesulfonic acid and sulfuric acid give a product with essentially a constant specific ethanol rotation of about $[\alpha]_D-265^{\circ}$, while mild isomerizing reagents such as very dilute ethanolic hydrochloric acid give a product with essentially a constant specific rotation of about $[\alpha]_D-130^{\circ}$. Conditions of reaction also effect rotation, vigorous conditions, for example, giving compositions of high rotation. Compositions may be obtained as indicated hereinafter giving fractions with rotations

ranging somewhere between the two limiting figures just mentioned. They are believed to be mixtures Of the $[\alpha]_D -130^\circ$ and 265° isomers. All of the tetrahydro cannabinol products thus formed, however, regardless of the specific rotation, have a marihuana activity and manifold the activity of purified red oil.

The lower rotating tetrahydrocannabinols can be readily converted to the higher rotating form by means of the same treatments which convert cannabidiol to the higher rotating form. For this reason it appears that a mere shift in the double bond is occurring, i. e., that the low and high rotating forms differ in the position of the double bond in the left-hand or hydro cycle.

The present invention is directed broadly to all materials obtained by isomerization of cannabidiol, the exact position of the double bond in the product being of relatively minor importance. The tetrahydro cannabinols obtained are colorless, highly viscous oils, though it is not impossible that eventually when one or more are obtained in absolutely pure state they will be found to be solids.

The tetrahydro cannabinols form acyl derivatives, such as the monoacetates, and ether-derivatives such as the monomethyl ether, with specific rotations corresponding to the rotation of the tetrahydro cannabinol from which each may be formed.

When the tetrahydro cannabinols are reduced, regardless of the specific rotation of the initial material used, after absorption of one molecule of hydrogen a hexahydro cannabinol is produced.

This product has a $[\alpha]_{27} D -70^\circ$; is physiologically active.

Formation of Tetrahydrocannabinols by Isomerization of Cannabidiol

A. By *p*-toluenesulfonic acid

A solution of about 0.19 gram of *p*-toluenesulfonic acid monohydrate and 3.14 grams of crystalline cannabidiol in 100 cc. of dry benzene was refluxed for one and one-half hours. At the end of that time the alkaline beam test was negative. The benzene solution was extracted twice with about 5% aqueous bicarbonate solution and twice with water. The benzene was then evaporated and the residue distilled under reduced pressure. Four fractions were collected. B.P. $169-172^\circ$ (0.03 mm.), having essentially the same rotation, $[\alpha]_{29} D -264^\circ$ to -270°

B. By sulfuric acid

To a solution of 1.94 grams of crystalline cannabidiol in 35 cc. of cyclohexane (free from unsaturated material) was added one drop of 100% sulfuric acid. The mixture was refluxed for one hour, at the end of which time the alkaline Beam test was negative. The solution was decanted from the sulfuric acid, washed twice with aqueous 5% bicarbonate solution and twice with water, and evaporated. The residue was distilled under reduced pressure. Three fractions were collected, B. P. 165-170° (0.1 mm.), $[\alpha]_{29D}$ —259° to—269°. Rotation.—0.0381 gram made up to 5 cc. with acetone at 29° gave $[\alpha]_D$ —210°; 1, 1; $[\alpha]_{29D}$ —264°.

C: By pyridine hydrochloride

A mixture of 6 g. of dry pyridine hydrochloride and 3 g. of cannabidiol (M. P. 66-67°) was heated at 125° for one hour. The Beam test (purple color with 5% alcoholic potassium hydroxide) had entirely disappeared after a relatively short time. The product was then washed with water to free it from pyridine hydrochloride, extracted with ether and the ether solution washed with water. After evaporation of the solvent, the product was distilled in high vacuo, whereupon hydrogen chloride was evolved. The distillate was a highly viscous, colorless oil with a B.P. approximately the same as that reported in the experiments using hydrochloric acid in ethanol for cyclization. Upon separating into six fractions, the specific rotations were as follows: $[\alpha]_{32D}$ —235°, - 236°, - 235°, —241°, —244°, —249°.

Rotation.—(Fraction 1) 0.0314 g. made up to 5 cc. with 95% ethanol at 32° gave a_D —2.95°; $[\alpha]_{32D}$ —235°

D: By phosphoric acid

A mixture of 3 g. of cannabidiol (M.P. 65-67°), 150 cc. of ethanol and 50 cc. of syrupy phosphoric acid (85%) was refluxed for thirty-five minutes. The Beam test was negative. The reaction solution was then poured into water and the product extracted with ether. Six fractions were collected in distillation, all of which gave essentially the same specific rotation, $[\alpha]_{26D}$ —160°. This product appears, therefore, to be the same as that prepared by the example ethanolic hydrochloric acid method.

Rotation.—(Extraction 3) 0.0481 g. made up to 5 cc. with 95% ethanol at 26° gave a_D —1.54; $[\alpha]_{26D}$ —160°

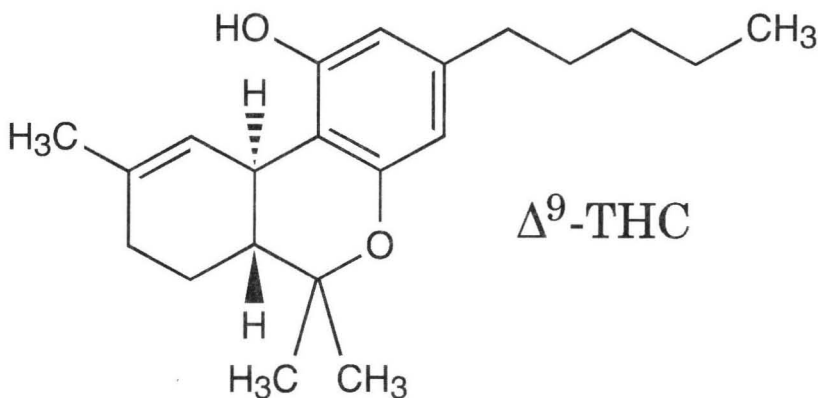
If the reaction mixture was refluxed two hours instead of thirty-five minutes with the proportions 3 g. of cannabidiol, 55 cc. of ethanol, 20 cc. of syrupy phosphoric acid (85%), a product was obtained which gave fractions with specific rotations varying from -188° to -199° . Upon refluxing one of these fractions for twelve hours with ethanol and phosphoric acid, the product gave a specific rotation of -179° .

It is obvious that changes are taking place within the molecule by the treatments just described. Investigations indicate the changes to be due to shifting of the double bond or interchange of stereoisomers or both.

E: Sulfamic acid; zinc chloride

Processes employing sulfamic acid or zinc chloride follow the general process described above. Upon heating cannabidiol with these reagents, the Beam test rapidly disappeared. From a sulfamic acid experiment at 125° (0.5 g. of cannabidiol, 1 g. of sulfamic acid), the product gave a specific rotation of -250° .

It will be obvious to those skilled in the art that the present invention is directed to the treatment of red oil (obtained from hemp and preferably American hemp) as well as the treatment of isolated cannabidiol. For example, a product of increased activity or potency may be obtained by treating purified red oil obtained from Minnesota wild hemp so as to isomerize the cannabidiol contained therein to tetrahydrocannabinol. It will also be understood by those skilled in the art that the present invention is not limited to any particular acid isomerizing agent or process. Source: Adams 1947



Converting *cis*-Hexahydrodibenzo[b,d]pyran-9-ones to *trans*-Hexahydrodibenzo[b,d]-pyran-9-ones

by William B. Blanchard of Indianapolis, IN
and Charles W. Ryan of Indianapolis, IN

July 6, 1976

Reaction of *cis*-1-hydroxy-3-substituted-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-ones with an aluminum halide in an unreactive organic solvent effects complete epimerization to provide the corresponding *trans*-1-hydroxy-3-substituted-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one.

In accordance with the present invention, a 6a,10a-*cis*-1-hydroxy-3-substituted-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one is reacted with an aluminum halide selected from the group consisting of aluminum chloride and aluminum bromide in an unreactive organic solvent to provide the corresponding 6a,10a-*trans*-1-hydroxy-3-substituted-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one. While the precise amount of aluminum halide required to effect such conversion is not particularly critical to the process, the epimerization reaction typically is accomplished by commingling the above-named 6a,10a-*cis*-dibenzo[b,d]pyranone derivative with an excess of the aluminum halide. The excess of aluminum halide routinely utilized in the reaction is an amount in the range of from about a 3 to about a 4 molar excess; however, even a larger excess can be utilized if desired. The reaction generally is carried out in an unreactive organic solvent. Typical examples of which include halogenated hydrocarbons such as chloroform, carbon tetrachloride, dichloromethane, bromomethane, 1,2-dichloroethane, bromoethane, bromobenzene, and chlorobenzene; aromatic solvents such as benzene, toluene, nitrobenzene, and xylene; as well as ethers such as diethyl ether and methyl ethyl ether. While the particular solvent utilized in the epimerization reaction of this invention is not of a critical nature, preferred solvents include the halogenated hydrocarbons such as dichloroethane, dichloromethane, bromoethane, and 1,2-dibromoethane; and aromatic solvents such as benzene and toluene.

The process for isomerization of a 6a,10a-*cis*-hexahydro-dibenzo[b,d]pyranone to the corresponding 6a,10a-*trans* isomer provided by this invention can be carried out within essentially any convenient reaction temperature range, since the precise reaction temperature is not of a critical nature to the process. The process typically is carried out at a temperature within the range of from about -80° to about 100° C., and preferably is conducted at a temperature within the range of from about 0° C. to about 50° C. The reaction time is also not critical to the process. While the reaction is normally substantially complete after about 10 minutes to 6 hours, longer reaction times are apparently not detrimental to the 6a,10a-*trans*-product which is formed. Routinely, the reaction is continued until the isomerization of the *cis*-dibenzo[b,d]pyranone to the corresponding *trans*-dibenzo[b,d]pyranone is substantially complete, for example as demonstrated by monitoring the progress of the reaction by normal methods such as thin layer chromatographic analysis. After the conversion of the *cis*-isomer to the desired *trans*-isomer is complete, the product is readily isolated by removal of any excess aluminum halide, for instance by washing the reaction mixture with water or with an aqueous acid solution such as dilute aqueous hydrochloric or sulfuric acid. The solvent can then be removed from the reaction mixture, for instance by evaporation, thus providing the desired 6a,10a-*trans*-1-hydroxy-3-substituted-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one, generally as one *dl*-mixture. The product thus formed is substantially free of foreign contaminants but can be further purified if desired by conventional techniques such as solid-liquid chromatography, thick-layer chromatography, and recrystallization from common solvents such as hexane and cyclohexane.

dl-trans-1-Hydroxy-3-(1,1-dimethyl-heptyl)-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one

A solution of 1.0 g. of *dl-cis*-1-hydroxy-3-(1,1-dimethylheptyl)-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one in 40 mL. of commercial grade dichloromethane was stirred at 24° C. while 1.0 g. of aluminum chloride was added in one portion. The reaction mixture was stirred at 24° C. for five hours. The reaction mixture was then washed with 1N hydrochloric acid solution and with water. After drying the organic solution, the solvent was removed therefrom by evaporation

under reduced pressure, providing 994 mg. of the product as a solid. The solid so formed was recrystallized from hexane to afford 761 mg. of *dl-trans*-1-hydroxy-3-(1,1-dimethylheptyl)-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one. M.P. 160°-161° C.

***dl-trans*-1-Hydroxy-3-n-pentyl-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one**

A solution of 400 mg. of *dl-cis*-1-hydroxy-3-n-pentyl-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one in 200 mL. of dichloromethane containing 1 mL. of cyclohexane was stirred at 24° C. while 600 mg. of aluminum chloride was added in one portion. The reaction mixture then was stirred at 24° C. for two hours. After washing the reaction mixture with water and then drying the organic solution, the solvent was removed by evaporation under reduced pressure, leaving the product as a solid. The solid so formed was crystallized from *n*-hexane to afford 220 mg. of *dl-trans*-1-hydroxy-3-n-pentyl-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one. M.P. 146°-150° C. nmr (CDCl₃) 67 Hz (s, 3H, C-6 methyl), 88 Hz (s, 3H, C-6 methyl).

***dl-trans*-1-Hydroxy-3-(1,1-dimethylheptyl)-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one**

To a solution of 1.0 g. of *dl-cis*-1-hydroxy-3-(1,1-dimethylheptyl)-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one in 40 mL. of dichloromethane was added in one portion 1.0 g. of aluminum bromide. The reaction mixture was stirred for five hours at 24° C., and then was washed with 1N hydrochloric acid solution and with water. The reaction mixture was dried and the solvent was removed by evaporation under reduced pressure, thus providing *dl-trans*-1-hydroxy-3-(1,1-dimethylheptyl)-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one. nmr (CDCl₃) 67 Hz (s, 3H, C-6 methyl), 88 Hz (s, 3H, C-6 methyl). Source: Blanchard 1977

Stereoselective Preparation of Hexahydrodibenzopyranones and intermediates therefor

by Robert A. Archer of Indianapolis, IN and
William A. Day of Indianapolis, IN

November 10, 1976

(-)-*trans*-1-Hydroxy-3-(1,1-dimethyl-heptyl)-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one

A solution of 77 mg. of (-)-*cis*-1-hydroxy-3-(1,1-dimethylheptyl)-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one in 5 mL. of dichloromethane containing 77 mg. of aluminum chloride was stirred at 25° C. for four hours. The reaction mixture then was diluted with 20 g. of ice, and the resulting aqueous mixture was extracted with diethyl ether. The ethereal extracts were combined, washed with 2N hydrochloric acid and with ten percent aqueous sodium bicarbonate solution, and then washed with water, dried, and the solvent was removed by evaporation under reduced pressure to provide 75 mg. of the product as an oil. The oil so formed was chromatographed over a thick layer silica gel coated plate. Elution of the principle band with a twenty percent solution of ethyl acetate in benzene, and evaporation of the solvent therefrom, afforded 54 mg. of (-)-*trans*-1-hydroxy-3-(1,1-dimethylheptyl)-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one. $[\alpha]_{20D} - 53.8^\circ$ ($c = 1.0$, CHCl₃).

Other References

Razdan et al., *Tetrahedron Letters*, pp. 4947-4950, (1969).

Source: Archer 1978

Many compounds (THC type) are well known, and others can be manufactured in accordance with published methods (see, for example, International Patent Application WO99/20268 (Burstein), and *U.S. Pat.* No. 2,509,386 (Adams). *U.S. Pat.* No. 3,799,946 (Loev), *U.S. Pat.* No. 3,856,821 (Loev), *U.S. Pat.* No. 3,897,306 (Vidic et al.), *U.S. Pat.* No. 4,064,009 (Fukada et al.). *U.S. Pat.* No. 4,087,545 (Archer et al.), *U.S. Pat.* No. 4,142,139 (Bindra), *U.S. Pat.* No. 4,309,545 (Johnson), *U.S. Pat.* No. 4,599,327 (Nograddi et al.), *U.S. Pat.* No. 4,833,073 (McNally et al.), *U.S. Pat.* No. 4,876,276 (Mechoulan et al.). *U.S. Pat.* No. 4,973,603 (Burstein), *U.S. Pat.* No. 5,338,753 (Burstein et al.), *U.S. Pat.*

No. 5,389,375 (ElSohly), *U.S. Pat.* No. 5,440,052 (Makriyannis et al.), *U.S. Pat.* No. 5,605,906 (Lau), and *U.S. Pat.* No. 5,635,530 (Mechoulam et al.), and Charalambous et al., *Pharm. Biochem. Behav.*, 40, 509-12 (191), Gareau et al., *Bioorg. Med. Chem. Lett.*, 6(2), 189-94 (1996), Griffin et al., *Br. J. Pharmacol.*, 126, 1575-84 (1999), Huffman et al., *Bioorg. Med. Chem. Lett.*, 6, 2281-88 (1998), Lemberger et al., *Clin. Pharmacol. Ther.*, 18(6), 720-26 (1975), Loev et al., *J. Med. Chem.*, 16(11), 1200-06 9 (1973). Loev et al., *J. Med. Chem.*, 17(11), 1234-35 (1974), Martin et al., *Pharm. Biochem. Behav.*, 46, 295-301 (1993), Papahatjis et al., *J. Med. Chem.*, 41(7), 1195-1200(1998), Pars et al., *J. Med. Chem.*, 19(4), 445-53 (1976), Pertwee et al., *Pharmacol. Ther.*, 74(2), 129-80 (1997), Razdan et al., *J. Med. Chem.*, 19(4), 454-60 (1976), Razdan, *Pharmacol. Reviews*, 38(2) 75-149 (1980), Reggio et al., *J. Med. Chem.*, 40(20), 3312-18 (1997). Reggio et al., *Life Sci.*, 56(23124), 2025-32 (1995), (Ross et al., *Br. J. Pharmacol.*, 126, 665-72 (1999), Thomas et al., *J. Pharm. Exp. Ther.*, 285(1), 285-92 (1998), Wiley et al., *J. Pharm. Exp. Ther.*, 285(1), 995-1004 (1998), Winn et al., *J. Med. Chem.*, 19(4), 461-71 (1976), and Xie et al., *J. Med. Chem.*, 41, 167-74 (1998)).

In the preferred embodiment wherein ring C of Formula III is aromatic, such compounds additionally can be manufactured by aromatizing an appropriate tetrahydrocannabinol (THC) derivative molecule by known methods (see, e.g., Adams et al., *J. Am. Chem. Soc.*, 62, 23401 (1940); Ghosh et al., *J. Chem. Soc.*, 1393 (1940); and Adams et al., *J. Am. Chem. Soc.*, 70, 664 (1948)). For example, aromatization of such compounds can occur by heating the compound with sulfur at about 238-240° C., under a nitrogen atmosphere, for about 4 hours (Rhee et al., *J. Med. Chem.*, 40(20), 3228-33 (1997)). Other suitable methods include aromatization using a catalyst (e.g., palladium on carbon) or a chemical dehydrogenating agent (e.g., 2,3-dichloro-5,6-dicyanoquinone) (see, for example, U.S. Pat. No. 3,799,946 (Loev)). Source Travis 2001

Acetylation of THC

Preparation of 1-Acetoxy-7,8,9,10-tetrahydro-3-(1-methylhexyloxy)-6,6,9-trimethyl-6H-dibenzo[b,d]pyran

by Bernard Loev of Broomall, Pa. July 18, 1973

A solution of 1.0 g. of 1-hydroxy-7,8,9,10-tetrahydro-3-(1-methylhexyloxy)-6,6,9-trimethyl-6H-dibenzo[b,d]pyran in 20 mL. of acetic anhydride containing 0.5 g. of sodium acetate is refluxed for 5 hours. The excess anhydride is evaporated in vacuo and the residue is dissolved in water and extracted with ether. The extract is washed with water

until neutral, then dried and evaporated to give an oil which is chromatographed on a silica gel dry-column. Concentration of the eluent and distillation of the residue in vacuo give the title compound.

Source: Loev 1974

Preparation of *dl-trans*-1-Acetoxy-3-(1',1'-dimethylheptyl)-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one:

By Robert A. Archer of Indianapolis, IN

Louis Lemberger of Indianapolis, IN

February 17, 1976

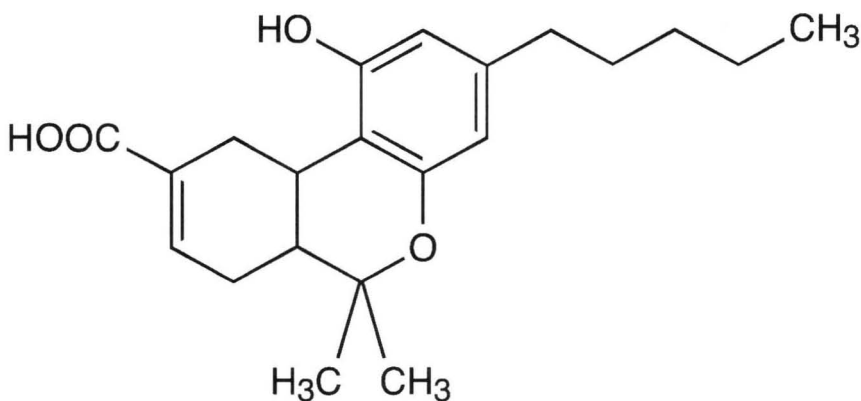
A mixture of 500 mg. of *dl-trans*-1-hydroxy-3-(1',1'-dimethylheptyl)-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one, 5 mL. of acetic anhydride, and 5 mL. of pyridine was stirred under an inert atmosphere for 16 hours. The mixture was then poured onto ice and extracted with ethyl acetate. The ethyl acetate extract was washed with 1 N HCl and saturated sodium chloride solution, dried over anhydrous sodium sulfate and evaporated in vacuo to give 450 mg. of *dl-trans*-1-acetoxy-3-(1',1'-dimethylheptyl)-6,6-dimethyl-6,6a,7,8,10,10a-hexahydro-9H-dibenzo[b,d]pyran-9-one as a viscous oil: R_f=0.33(Silica gel, 10% Ethyl acetate:benzene): IR (CHCl₃) 5.62, 5.80, and 8.28 μ ; molecular ion at m/e 414.

As previously mentioned, compounds represented by Formula IV above have the ability to produce bronchodilation in humans and can alleviate bronchial asthma in man. Bronchial asthma, including both extrinsic or allergic asthma and intrinsic or infective asthma, is characterized by recurrent paroxysms of dyspnea associated with a characteristic type of wheezing caused by obstruction of the flow of air in the smaller bronchi and bronchioles. In more severe attacks, trapping of air in the alveoli may occur, completely obstructing the airways, which event may result in death. Drugs represented by Formula IV above appear to act to alleviate asthmatic symptoms by relaxing bronchial smooth muscle thereby increasing the passage of air from the lung. They may also act, in part, by a central mechanism relieving anxiety, a major component of this disease. Source: Archer 1978; Johnson 1980

Chapter 8: Delta 1-THC-7-oic acid Analgesic and Anti-inflammatory Agents Metabolites of Δ^1 -Tetrahydrocannabinol

by Sumner Burstein of Framingham, MA

August 17, 1987



Tetrahydrocannabinol-7-oic Acid

Δ^1 -Tetrahydrocannabinol (THC) (Formula I) is the major psychoactive constituent of marijuana (Hollister, L.E. *Science*, 172:21-29, 1971; Isbell, H., Gorodetsky, C. W., Jasinski, D., Claussen, V., von Spulak, F. and Korte, F. *Psychopharmacologia*, 11:184-188, 1967; Mechoulam, R., *Science*, 168:1159-1166, 1970). The initial metabolites of THC are monohydroxy derivatives active as mood-altering agents. It is believed that these monohydroxy derivatives of THC contribute to the overall effects of the drug, but their presence is not required for the psychotropic action of cannabis (Harvey, D. J. and Paton, W. D. M. *Rev. Biochem. Toxic.* 6:250, 1984).

Metabolism of the monohydroxy THC derivatives involves a series of oxidative transformations that ultimately leads to a group of carboxyl-containing derivatives of the parent substance. These acidic metabolites were thought to display none of the biological activities of their precursors and have been generally regarded as inactive metabolic end-products.

The most abundant member of this group is the cannabinoid Δ^1 -THC-7-oic-acid. When tested in humans as well as in the rhesus monkey, this cannabinoid did not show the behavioral activity or the cardiovascular effects characteristic of the parent substance, THC. (Perez-Reyes, M. In: *Pharmacokinetics and Pharmacodynamics of Psychoactive Drugs*, Barnett, G. and Chiang, N. (eds), Biomedical Press, 1985, pages 287-310; Mechoulam, R. and Edery, M. In: *Marijuana*, Mechoulam, R. (ed.), Academic Press, New York, 1973). Thus, little attention has been given to the possible pharmacodynamic properties of this metabolite or any of the other acid metabolites of THC.

It has long been known that THC possesses potent analgesic and anti-inflammatory properties. However, the biochemical bases for these effects was not well understood. Although it has been suggested that the THC-induced elevation of plasma corticosteroids was responsible, the experimental support for this hypothesis is inconclusive (Sophia, R. D., Nalepa, S. D., Harakal, J. J. and Vassar, H. B., *J. Pharma. Exper. Ther.* 186:646-655, and 1973). It has also been shown, in a variety of models that Δ^1 -THC-7-oic-acid can be a potent inhibitor of the prostaglandin synthetase system (Burstein, S., Hunter, S. A., Lathan, V. and Renzulli, L., *Biochem. Pharmac.* 35:2553-2558, 1986).

The Δ^1 -THC-7-oic-acid metabolite has also been shown to antagonize the in vitro action of the parent substance (Burstein, S., Hunter, S. A., Latham, V. and Renzulli, L. *Biochem. Pharmac.* 35: 2553-2558, 1986). The system in which this observation was made involved exposing cells in culture to cannabinoids and measuring the change brought about in the metabolism of arachidonic acid (Burstein, S., Hunter, S. A. and Ozman, K. *Molec. Pharmac.* 23:121, 1983; Burstein, S. and Hunter, S. A. *J. Clin. Pharmac.* 21:2405, 1981; Burstein, S. Hunter, S. A., Sedor, C. and Shulman, S. *Biochem. Pharmac.* 31:2361, 1982). The addition of the metabolite to the culture medium prior to THC exposure resulted in a dramatic lowering of the stimulatory effect of THC on prostaglandin synthesis. A kinetic and chromatographic analysis of the metabolic products in the media suggested that cyclooxygenase may be the site of inhibition by the Δ^1 -THC-7-oic acid (Burstein, S. et al., *Biochem. Pharmac.* 35:2553-2558, 1986).

This invention is based on the discovery that Δ^1 -THC-7-oic-acid is a potent analgesic and anti-inflammatory agent, and that when administered directly into the stomach is non-ulcerogenic. As a result, this non-psychoactive metabolite of THC can be used as a therapeutic agent for such purposes as the treatment of chronic pain and tissue inflammation often associated with illnesses such as rheumatoid arthritis.

The subject invention concerns a non-psychoactive metabolite of THC, Δ^1 -THC-7-oic-acid, which has been shown to be an active analgesic and anti-inflammatory agent. The invention is further related to the use of this metabolite as a therapeutic agent in the treatment of pain and tissue inflammation, especially that associated with long-term illnesses such as rheumatoid arthritis. It has been shown that this metabolite does not induce the gastrointestinal damage which accompanies the habitual use of the leading analgesics and nonsteroidal anti-inflammatory agents (NSAIDS) available today.

It has now been discovered that this metabolite, when administered to laboratory animals in a standard pharmacological assay for analgesia (see exemplification), produces a pain-relieving effect which is merely equivalent to that of naproxen (6-Methoxy- α -methyl-2-naphthaleneacetic acid), a popular analgesic and anti-inflammatory agent in use today. Thus, the therapeutic effects of the Δ^1 -THC-7-oic-acid metabolite can be separated from the psychoactive effects of THC, the parent substance.

One common adverse effect of the consumption of NSAIDS is gastrointestinal damage, generally as bleeding and/or frank ulceration. A frank ulcer is a necrotic lesion, usually elongated, which penetrates the gastric mucosa and resists removal by wiping or rinsing with physiological saline. The therapeutic agent of this invention is non-ulcerogenic. In a standard pharmacological assay for ulcerogenicity it was discovered that the Δ^1 -THC-7-oic-acid metabolite did not induce ulcer formation. That is, its administration directly into the stomach did not result in ulcer formation in any rats to which it was given. This result is in sharp contrast to the effects of aspirin which, when given in half the therapeutic dose, induced the formation of gastric lesions in each test animal.

Δ^1 -THC-7-oic-acid, which is a non-psychoactive metabolite of THC, has been shown to retain the analgesic and anti-inflammatory properties of THC and to be non-ulcerogenic. This metabolite is especially useful as a therapeutic agent in the treatment of chronic pain and inflammation associated with long-term illnesses, such as rheumatoid arthritis, in which individuals must consume needed drugs over extended periods of time. Δ^1 -THC-7-oic-acid produces the desired analgesic and anti-inflammatory effects without subjecting the individual to the risk of developing gastric ulcers, as occurs during habitual consumption of presently available drugs (e.g., aspirin, naproxen and indomethacin).

This therapeutic agent can be used in both veterinary medicine and in human therapy. For human therapy a preferred method of administering Δ^1 -THC-7-oic-acid would be orally in the form of a

gelatin capsule. The dosage of the metabolite according to this invention generally is 10 to 500 mg/70 kilograms (kg) of body weight/day, preferably 50 to 150 mg/70 kg/day. The actual preferred amounts of active compound in a specific case will vary, of course, according to the particular species of mammal afflicted, the severity of the inflammation and the actual method of administration.

In addition to its analgesic and anti-inflammatory properties, THC is known to be useful as an antiemetic (especially against nausea and vomiting caused by cancer chemotherapeutic agents; Sallan, S. E., Cronin, C., Zelen, M. and Zinberg, N. E. *N. Eng. J. Med.*, 302:135-138, 1980) and as a bronchodilator for asthmatics. Thus, the metabolite, Δ^1 -THC-7-oic-acid, may possess these same properties. Furthermore, Δ^1 THC-7-oic-acid may be an effective therapeutic agent in treating fever because analgesic, anti-inflammatory and antipyretic properties are often associated with one another.

This invention has a further application in the area of medicinal chemistry where Δ^1 -THC-7-oic-acid can be used as a model to design similar or more efficacious synthetic analogs for relieving pain and tissue inflammation in mammals. An analog is a compound that resembles another in structure. For example, an analog of Δ^1 -THC-7-oic-acid may have a modification in one or more of the rings and one or more of its substituents alone or in combination.

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Source: Burstein 1989

Platelet Activating Factor Antagonist

by Burstein; Sumner

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May 11, 1989

Platelet activating factor (PAF) has been identified as 1-O-alkyl-2-O-acetyl-sn-glycero-3-phosphocholine. Many different types of mammalian cells have been reported to release PAF upon stimulation. F. H. Chilton et al., *Journal of Biochemistry*, 257:5402-5407 (1982).

Platelet activating factor (PAF) is an endogenous lipid which has been implicated in a number of adverse pathological consequences due to disease and/or environmental occurrences. P. Braquet, L. Touqui, T. Y. Shen and B. B. Vargaftig, *Pharmacol. Revs.* 39:97-145(1987). These include platelet-induced thrombosis, acute inflammation, asthma and systemic anaphylaxis, transplant rejection, cardiac anaphylaxis, kidney physiology and immune disorders, endotoxic and IgG-induced shock, gastrointestinal ulceration, inflammatory and allergic skin diseases, retinal and corneal diseases, neuronal degradation, panic disorders and failure of ovoimplantation. An intensive search has been in progress in recent years to discover and develop drugs which will effectively control these adverse effects of PAF. Thus far, no agents of this type have been made available for general use in treating PAF-induced medical problems.

This invention relates to the discovery that 6a,7,10,10a-tetrahydro-6,6-dimethyl-9-carboxyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol is a potent antagonist to the actions of PAF. A composition containing this compound is administered to a subject for treatment of various disorders induced by PAF. The composition can be used as a therapeutic agent for the treatment of PAF-mediated disorders such as asthma or other pulmonary dysfunction, systemic anaphylaxis, transplanted organ rejection, septic shock, gastrointestinal ulceration, allergic skin diseases, and acute inflammation. The composition of the invention can be administered orally or parenterally to a subject in an amount sufficient to substantially inhibit the actions of PAF, thereby reducing the symptoms caused by PAF. When administered directly into the stomach, the present composition is non-ulcerogenic, and thus does not induce the gastrointestinal damage which accompanies the chronic use of PAF antagonists currently available.

Formula I is a naturally occurring derivative of the compound 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-

ol which is a minor component of *Cannabis sativa*. R. Mechoulam, Z. Ben-Zvi, S. Agurell, I. M. Nilson, J. L. G. Nilson, H. Edery and Y. Grunfeld, *Exper.* 29:1193-1195 (1973). Formula I is formed from this compound by a series of biotransformations mediated primarily by mammalian liver enzymes.

One common adverse effect of the consumption of currently available PAF antagonists, such as naproxen and phenidone, is gastrointestinal damage, generally manifested as bleeding and/or frank ulceration. A frank ulcer is a necrotic lesion, usually elongated, which penetrates the gastric mucosa and resists removal by wiping or rinsing with physiological saline. The composition of this invention is non-ulcerogenic. In a standard pharmacological assay for ulcerogenicity, it was shown that Formula I did not induce ulcer formation. Administration of the present composition directly into the stomach did not result in ulcer formation in any rats to which it was given. This result is in contrast to the effects of aspirin, which, when given in half the therapeutic dose, induced the formation of gastric lesions in each test animal.

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Source: Burstein 1990

Non-psychoactive Derivatives of Δ 6-THC-7-oic Acid which have Analgesic and Anti-inflammatory Properties

by Sumner H. Burstein of Framingham, MA
Raphael Mechoulam of Jerusalem, IL

July 14, 1992

Previous work with Δ 6-Tetrahydrocannabinol [(3R,4R) 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol, hereinafter referred to as Δ 6-THC], has indicated that derivatives of this compound may prove clinically useful. The 7-carboxy derivative of Δ 6-THC [Δ 6-THC-7-oic acid] has been reported to be a non-psychoactive, potent antagonist to endogenous platelet activating factor and, thus, a useful treatment for PAF-induced disorders, such as asthma, systemic anaphylaxis, and septic shock. (*U.S. Pat.* No. 4,973,603, issued Nov. 27, 1990 to Sumner Burstein). Another derivative, (3S,4S)-7-hydroxy- Δ 6-THC-1,1-dimethylheptyl, has been reported to possess analgesic and anti-emetic activities. (*U.S. Pat.* No. 4,876,276).

The present invention is generally directed to non-psychoactive derivatives of Δ 6-THC-7-oic acid, which have been shown to be potent analgesic and anti-inflammatory agents and to possess leukocyte antiadhesion activities. The invention is further related to the use of these derivatives as therapeutic agents in the treatment of pain and tissue inflammation, especially that associated with long-term illnesses such as rheumatoid arthritis.

Synthesis of (3R,4R)- Δ 6-THC-DMH-7-oic Acid Acetate (3c).

A solution of acid 3a (100 mg, 0.25 mmol) in pyridine (2 mL) and acetic anhydride (1 mL) was stirred overnight at room temperature. Water (5 mL) was added to hydrolyze any mixed anhydride formed. The mixture was stirred for two (2) hours and then partitioned between water and ether. The ether layer was washed with dilute HCl (to remove the pyridine) and water. The organic layer was dried and evaporated. Pure product was obtained by preparative TLC (eluent ether-petroleum ether, 60:40) and crystallization from pentane. The acetate 3c, 65 mg, melts at 120°-122° C.: $[\alpha]_D^{25}$ -265° (c 9.0 mg/mL, CHCl₃)

Source: Burstein 1994 Reference: Mechoulam 1996



Anandamide



Oleamide

Chapter 9: Andanamides Fatty Acid Amides

by Raphael Mechoulam, Aviva Beuer and Lemir Hanus of Jerusalem, Isreal and William A. Devane of Chevy Chase, Maryland

November 30, 1993

Pure polyunsaturated fatty acid amides and their derivatives. These synthcally produced compounds are able to mimic naturally occuring anandamides in the brain and bind the cannabinoid receptor. The compounds exhibit physiological activity and are useful as active ingredients in pharmaceutical compositions for the treatment of inflammation, migraines, spasticity activity, glaucoma, multiple sclerosis.

Arachidonic acid ethanolamide (anandamide) and similar compounds are constituents of the brain. Anandamide and certain of the compounds similar with same, bind to the cannabinoid receptor. The binding of the ananamide to the cannabinoid receptor is similar to the binding of Δ^9 -tetrahydrocannabinol. There exist in the body many mediators, which are derivatives of arachidonic acid, such as prostaglandins and leukotrienes, which are present as large families of related compounds. Certain of these do not bind to the cannabinoid receptor, and it was one of the aims of the present invention to provide and identify compounds which have pharmacological properties similar to the properties of anandamide.

The existence of a receptor and the high structural requirements for cannabinoid activity indicate the possible presence of a specific endogenous cannabinoid ligand.

Endogenous ligands for the cannabinoid receptor have not yet been identified. Arachidonylethanolamide, a new arachidonic acid derivative named anandamide, was isolated from porcine brain. Its structure was determined by mass spectrometry and nuclear magnetic resonance spectroscopy and was confirmed by synthesis. It inhibits the specific binding of a labelled cannabinoid probe to synaptosomal membranes in a manner typical of competitive ligands, and produces a concentration-dependent inhibition of the electrically-evoked twitch response of the mouse vas deferens, a characteristic effect of psychotropic cannabinoids. Similar compounds were synthesized and their pharmacological properties were investigated.

Δ^9 -Tetrahydrocannabinol (Δ^9 -THC), the psychoactive constituent of *Cannabis* binds to a specific G-protein coupled receptor in the brain. Although the cannabinoid receptor in the rat and in the human has been cloned, its physiological function is unknown. The well established behavioral effects of THC and the abundance and anatomical localization of the receptor in the brain suggest a role for the receptor in the control of movement, memory, emotions and pain modulation, amongst other activities.

The existence of a receptor and the high structural requirements for cannabinoid activity indicate the possible presence of a specific endogenous cannabinoid ligand.

A compound was recovered (0.6 mg from 4.5 kg of brain), named anandamide, which shows one spot on tlc and elutes mainly as one peak on gas chromatography (GC) using a mass spectrometer as a detector. Anandamide inhibits the specific binding of [3 H]HU-243 to synaptosomal membranes in a manner typical of competitive ligands with a KD of 52 ± 1.8 nM ($n=3$) (FIG. 1). In this system the KD of Δ^9 -THC was 46 ± 3 nM.

Results from previous experiments, in which we compared the inhibitory effects of the 1,1-dimethylheptyl homologs of (+) and (-)-11-hydroxy- Δ^8 -tetrahydrocannabinol on the electrically-evoked twitch response of the mouse vas deferens, indicate that this preparation is suitable as a model for investigating the mode(s) of action of psychotropic cannabinoids. R. G. Pertwee, L. A. Stevenson, D. B. Elrick, R. Mechoulam, A. D. Corbett, *Brit. J. Pharmacol.* 105, 980 (1992). Anandamide produced a concentration-dependent inhibition of the twitch response (FIG. 2). The inhibition was not reversed by naloxone (300 nM). The levels of inhibition are comparable to those of binding to the receptor.

The structure of anandamide was established by mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy. Additional data were obtained from the GC-MS and CID measurements of the trimethylsilyl (TMS) derivative of the material. The results suggest that anandamide is an ethanolamide of a tetraenic C20 fatty acid.

Support for the above structure was found in the behavior of anandamide under GC-MS conditions.

Preparation of Arachidonyl Ethanolamide

A juxtaposition of the above analytical data led us to conclude that the structure of anandamide is that of arachidonyl ethanolamide [5,8,11,14-icosatetraenamide, (N,-2-hydroxyethyl)-(all-Z)] a novel chemical entity. This conclusion was confirmed by synthesis. Arachidonyl chloride, prepared from arachidonic acid and oxalyl chloride (21), in methylene chloride, was added at 0 degrees C., under a nitrogen atmosphere to ethanolamine (in a ten fold molar excess) in methylene chloride. After 15 min the reaction was washed with water, dried, and the product (ca 90% yield) was purified by silica column chromatography (eluted with 2% methanol in chloroform) to give archidonylethanolamide, an oil, in 97% purity (by GC-MS). Synthetic arachidonylethanolamide was identical with the product obtained on tlc (10), NMR (300 MHz) and GC-MS (retention time and fragmentation pattern) (FIG. 3). Synthetic anandamide binds to the cannabinoid receptor $KI = 39 \pm 5.0$ nM (n=3).

The novel purified compound anandamide seems to be present as brain constituent. It is possible that this compound is present as a complex with another compound or in any other form, but according to the present invention it has been established that the compound defined herein as ananamide is characterized by the properties set out herein. Similar compounds, defined herein, are characterized by essentially equivalent properties.

Following the synthetic method described for arachidonyl-ethanolamide, the ethanolamides of the following unsaturated fatty acids were prepared.

Systematic Name	Trivial Name	Shorthand designation
9,12-Octadecadienoic*	linoleic	18:2 (n-6)
6,9,12-Octadecatrienoic	Δ -linolenic	18:3 (n-6)
8,11,14-Eicosatrienoic	homo- Δ -linolenic	20:3 (n-6)
4,7,10,13,16-Docosapentaenoic	--	20:5 (n-6)
9,12,15-Octadecatrienoic	Δ -linolenic	18:3 (n-3)
5,8,11,14,17-Eicoisapentaenoic	--	20:5 (n-3)
4,7,10,13,16,19-Docosaheptaenoic	--	22:6 (n-3)
5,8,11-Eicosatrienoic	--	20:3 (n-9)

*The doublebond configuration in each instance is *cis*.

These ethanol amide derivatives have antiinflammatory analgetic, antiglaucoma and antiemetic activity.

The effective doses for humans are between 1-100 mg total daily dose, by injection or by oral administration.

TABLE I

Analgesia and Vomiting Reduction

Compound	Analgesia ED50 (mg/kg)	Reduction of vomiting (50%) (mg/kg)
Arachidonylethanolamide	4.2	2.5
5,8,11,14,17-Eicosapentaenyl ethanolamide	5.2	3.6
4,7,10,13,16,19-Docosa- hexaenylethanolamide	6.1	4.8
5,8,11-Eicosatrienyl- ethanolamide	7.6	6.2

in mice. For details of administration see Text
in pigeons. For details of administration see Text.

TABLE II

Inhibition of Arachidonic Acid-Induced Paw Edema

Dose (mg/kg)(b)	Arachidonyl- ethanolamide	4,7,10,13,16,19 Docosahexaenyl ethanolamide
0.010	56.2	--
0.025	58.4	--
0.050	74.2	52.4
0.100	98.0	66.8
0.250	100.0	72.0

Values shown are percent inhibition of paw edema when compared to vehicle treated controls. 95% significance by ANOVA. N = 5 mice/group. (b) Control mice were given peanut oil (50 ul) orally. Paw volume increase = 38 + 4 ul.

COMPOUNDS ISOLATED FROM THE BRAIN AND SYNTHESIZED

Name of Compound	Ki
<i>cis</i> -7,10,13,16-Docosatetraenoylethanolamide	34.4 +- 3.2 nM
Anandamide	39.0 +- 5.0 nM
Linolenoylethanolamide	53.4 +- 5.5 nM

SYNTHETIC COMPOUNDS PREPARED AND TESTED

N-Propyl-5,8,11,14-eicosatetraenoylamide	11.7 +- 2.6 nM
N-Ethyl-5,8,11,14-eicosatetraenoylamide	34.0 +- 2.7 nM
N-Methyl-5,8,11,14-eicosatetraenoylamide	60.0 +- 7.4 nM
Arachidonoyl- β -dimethylethanolamide	161.8 +- 34.1 nM

Pharmaceutical compositions, containing as active ingredient an effective quantity of the compounds of the present invention, have a variety of pharmacological effects. Amongst these there may be mentioned anti-inflammatory, anti-asthmatic, analgetic, antiglaucoma, anti-migraine and anti-spasticity effects. They are also mood-stimulating and ameliorate the symptoms of multiple sclerosis. The unit dosage form varies according to the compound and medical use, and is generally in the range between about 1 mg to about 100 mg. The preferred range is between about 5 to about 25 mg per unit dosage form.

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Anandamide Amidase Inhibitors as Analgesic Agents

by Alexandros Makriyannis; Sonyan Lin; and William Adam Hill Ashford & Storrs, CT May 31, 1996

Disclosed is a method of inhibiting anandamide amidase in an individual or animal and novel inhibitors of anandamide amidase. The disclosed method and novel compounds can be used to reduce pain in an individual or animal suffering from pain, reducing nausea in an individual undergoing chemotherapy, for example cancer chemotherapy, suppressing appetite in an individual, reducing intraocular pressure in the eye of an individual or animal suffering from glaucoma and suppressing the immune system in an individual with an organ transplant.

Δ 9-Tetrahydrocannabinol, the psychoactive marijuana derived cannabinoid, binds to the CB1 receptor in the brain and to the CB2 receptor in the spleen. Compounds which stimulate the CB1 receptor have been shown to induce analgesia and sedation, to cause mood elevation, to control nausea and appetite and to lower intraocular pressure (Mechoulam, *Cannabinoids as Therapeutic Agents*, CRC Press, Boca Raton, Fla. (1986), Fride and Mechoulam, *Eur. J. Pharmacol.* 231:313 (1993), Crawley et al., *Pharmacol. Biochem. Behav.* 46:967 (1993) and Smith et al., *J. Pharm. Exp. Therap.* 270:219 (1994)). Cannabinoids have also been shown to suppress the immune system (Mechoulam, *Cannabinoids as Therapeutic Agents*, CRC Press, Boca Raton, Fla. (1986)). Thus, compounds which stimulate the CB1 or CB2 receptor, directly or indirectly, are potentially useful in treating glaucoma, preventing tissue rejection in organ transplant patients, controlling nausea in patients undergoing chemotherapy, controlling pain and enhancing the appetite and controlling pain in individuals with AIDS Wasting Syndrome.

Arachidonyl ethanolamide (anandamide) is a naturally-occurring brain constituent that acts as a CB1 and CB2 agonist and exhibits pharmacological activity in mice comparable to cannabinoids (Fride and Mechoulam (1993), Crawley et al. (1993) and Smith et al. (1994)). Anandamide is cleaved in vivo by anandamide amidase. Thus, inhibitors of anandamide amidase have the effect of indirectly stimulating the CB1 and CB2 receptors by increasing in vivo levels of anandamide. In addition to acting at the CB1 and CB2 receptors, cannabinoids also affect cellular membranes, thereby producing undesirable side effects

such as drowsiness, impairment of monoamine oxidase function and impairment of non-receptor mediated brain function. The addictive and psychotropic properties of cannabinoids also limit their therapeutic value. Inhibitors of anandamide amidase are not expected to have the undesired membrane-related side-effects produced by cannabinoids. By providing an alternate mechanism for stimulating the CB1 and CB2 receptor, anandamide inhibitors might not have the addictive and psychotropic properties of cannabinoids. However, present inhibitors of anandamide amidase have disadvantages. For example, phenylmethylsulfonyl fluoride (PMSF) is toxic to cells. Thus, there is a need for new and more potent inhibitors of anandamide amidase which have reduced toxicity towards cells.

The binding affinity of palmitylsulfonyl fluoride for the CB1 receptor is about 10 times lower than anandamide.

Source: Makriyannis 1997

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Treating Anxiety and Mood Disorders with Oleamide

by Thomas D. Geraciotti, Jr. and John W. Kasckow
Cincinnati, OH November 22, 2000

The mood and anxiety disorders in their various permutations constitute a major source of personal suffering and impaired ability to engage in productive work and interpersonal relationships. Between 5 and 9% of women and between 2 and 3% of men meet the diagnostic criteria for major depression at any time; 10-25% of all women suffer major depression sometime in their lives, while 5-10% of men will develop major depressive disorder (American Psychiatric Association, 1994). The anxiety disorders obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), panic disorder, and generalized anxiety disorder (GAD) show lifetime prevalence rates of approximately 2.5%, 7%, 2.5%, and 5% respectively. Between 3 and 13% of individuals in community samples are regarded to meet the diagnostic criteria for social phobia. Mood and anxiety disorders are common comorbidities (American Psychiatric Association, 1994) and the most common antidepressant medications including the serotonin reuptake inhibitors, the mixed serotonin-catecholamine reuptake inhibitors, the tricyclic antidepressants, and the monoamine oxidase inhibitors, are all effective treatments for anxiety and panic attacks.

Affective disorders, while characterized by depressed mood of varying degrees, exist in various forms. Thus, melancholic depression is characterized by continuously depressed mood and pervasive hopelessness, insomnia with early-morning awakening (with the inability to return to sleep), loss of appetite and weight loss, and excessive feelings of guilt (American Psychiatric Association, 1994). In contrast, so-called "atypical" depression is characterized by hypersomnia (oversleeping), hyperphagia and weight gain, and often mood reactivity. In general, regardless of whether or not the depressive syndrome is melancholic, atypical, or some admixture of the two a diagnosis of major depression is

given when depressed mood is present, or loss of interest or pleasure in all activities is present, for at least two weeks (American Psychiatric Association 1994). If less severe or incapacitating, depressed mood is considered dysthymia. Depressed mood can occur in the form of a cycling mood abnormality such as bipolar mood disorder, cyclothymia, or menstrual-related mood disorder.

Mood disorders are commonly seen in general medical practice and some general medical disorders resemble depression in important respects. In particular, both fibromyalgia and chronic fatigue syndrome are medical disorders that have clinical and pathophysiologic features in common with atypical depression.

It is widely accepted that the hypothalamic-pituitary-adrenocortical axis is dysregulated in patients with major depression. One of the early findings of biological psychiatry was that approximately 50% of depressed patients showed hypercortisolemia increased concentrations of the circulating steroid cortisol, produced by the adrenal cortex (Sachar 1967). This led to the hypothesis that the principle central nervous system (CNS) effector of the HPA axis, corticotropin-releasing hormone (CRH), was hypersecreted in depressed patients. Elevated levels of CRH in the cerebrospinal fluid (CSF) of depressed patients were subsequently observed, consistent with this hypothesis (Nemeroff et al 1984, Banki et al 1987, Arato et al 1989). Similarly, some patients with anxiety disorders, such as post-traumatic stress syndrome have elevated CSF levels of CRH (Baker et al 1999). However, it has also become appreciated that many depressed patients, with or without anxiety disorders, do not show hypercortisolemia and, in fact, show evidence of an insufficient or pathologically inactive hypothalamic-pituitary-adrenocortical axis (Casper et al., 1988, Vanderpool et al., 1991). These patients, most often the atypically depressed or eucortisolemic, have low CSF CRH levels (Geraciotti et al., 1992 & 1997). Evidence of low CRH activity has also been found in patients with chronic fatigue syndrome and fibromyalgia (Demitrack and Crofford 1998).

Mood and anxiety disorders very frequently coexist in the same individual. In this regard, it is now appreciated that almost all antidepressants improve anxiety symptoms. Conversely, the most popular anxiolytics, the benzodiazepines, improve mood acutely but are typically ineffective or harmful to mood during chronic use.

The current psychopharmacologic treatments of affective and anxiety disorders are limited. A significant portion of depressed patients are resistant to treatment with existing antidepressants or combinations thereof either because of non-responsiveness or because a positive effect wears off (breakthrough depression) or is inadequate (depression

in partial remission). Troubling side effects may also be seen with existing antidepressants. After beginning daily administration, psychopharmacologic anti-depressants at present have a latency of typically two weeks before the onset of significant antidepressant activity. As noted, antidepressant drugs are also used to treat anxiety disorders; the limitations of these drugs in treating anxiety are similar to those faced in attempts to treat depression: many patients are resistant to treatment or gain only partial or short-lasting responses; the common side effects are troubling (for example, the serotonin-reuptake inhibitors are the drugs most commonly used to treat unipolar depression and the most commonly used agents to treat obsessive-compulsive disorder; these agents may have significant, unwanted sexual and/or gastrointestinal side effects in both male and female patients among other side effects and are either ineffective or only partially effective in a substantial percentage of patients). The most commonly used anxiolytic medications, the benzodiazepines, have a number of major limitations: (a) tolerance to their effects rapidly develops, with increasing doses becoming required to achieve the same effect; (b) benzodiazepine dependence is a standard occurrence after chronic use; (c) major withdrawal syndromes are seen including grand mal seizures after abrupt discontinuation; (d) overdose is associated with respiratory depression and sometimes death; (e) effects are potentiated by alcohol, which is cross-tolerant with the benzodiazepines; and (f) high abuse potential.

Oleamide

Unsaturated fatty acid amides represent a unique class of signaling molecules within the central nervous system (Lerner et al 1994, Cravatt et al 1995, Basile et al 1999). The fatty acid amides appear to be simple molecules with a great deal of diversity based on differing alkane chain lengths, stereochemistry, and locations of double bonds (Cravatt et al 1995).

Oleamide, a lipid originally named “cerebrodiene,” was first isolated from partially sleep-deprived cats (Lerner et al 1994). The molecule, with the chemical formula $C_{18}H_{35}NO$, is a long-chain base structurally related to sphingosine and sphinganine (Lerner et al 1994). Oleamide, or cerebrodiene, is chemically characterized as *cis*-9,10-octadecenoamide (Cravatt et al 1995). Oleamide is degraded by the brain enzyme fatty acid amide hydrolase (FAAH), which also degrades anandamide (Cravatt et al, Nature 1996).

Synthetic *cis*-9,10-octadecenoamide induced 1-2.5 h of sleep in rats when injected intraperitoneally in doses between 5 and 50 mg (Cravatt et al 1995). Doses between 5 and 150 mg reduce sleep latency in rats while sleep-deprived rats develop two- to three-fold increases in CSF oleamide levels (Basile et al 1999).

Oleamide markedly potentiates 5-HT-elicited currents in oocytes expressing the rat 5-HT₂ receptor, probably as an allosteric regulator, but has no significant direct effects (Huidobro-Tora & Harris 1996). The parent compound oleic acid does not have any effect, indicating the necessary presence of the amide group. A related fatty acid, octadecanamide had effects on the 5HT receptor that were opposite those of oleamide (Huidobro-Tora & Harris 1996). In vivo evidence also suggests that oleamide indirectly potentiates 5HT₂ function (Cheer et al 1999). Oleamide had no significant effects on the ionotropic GABA-A, N-methyl-D-aspartate (NDMA), and 5HT₃ receptors. The possibility that lipid amides modulate other G-protein-coupled receptors is of great interest.

Conclusion

Our discovery that oleamide increases CRH mRNA and stimulates secretion of CRH from cloned hypothalamic cells and also increases exploratory behavior on the elevated plus maze, in combination with the earlier findings that CSF CRH levels are low in many patients with anxious major depression (Geraciotti et al., 1992 and 1997), and that brain CRH mRNA increases after use of the antidepressant treatment electroconvulsive therapy (Brady et al 1994), form the basis for administering oleamide or an inhibitor of its hydrolysis (including those oleamide hydrolase inhibitors that are disclosed in *U.S. Pat. No. 5,856,537*) to patients with depression and/or anxiety disorders. Conversely, the hyperactivity of CNS CRH in other patients with major depression (Nemeroff et al 1984) and some forms of anxiety disorder, such as post-traumatic stress disorder (Baker et al 1999), form the basis for the use of oleamide antagonists in these conditions. In this regard, several antidepressant agents cause reductions in CNS CRH concentrations or synthesis (Brady et al., 1991 & 1992). Source: Geraciotti 2002

See Boring 1996; Lerner 1994 for oleamide cannabinoid activity.
 Anti-cancer Activity See: Di Marzo *et al*; Palmitoylethanolamide Inhibits the Expression of Fatty Acid Amide Hydrolase and Enhances the anti-proliferative Effect of Anandamide in Human Breast Cancer Cells. *Biochem J.* (2001) 358 (Pt 1) :249-55.



Chapter 10: Fatty Acid Amides Preparation from Common Household Oils

Preparation of Oleamide (Cerebrodiene)

Oleic acid 56 grams (0.2 mole) and 36 grams (0.6 moles) urea are mixed and rapidly heated to 230 degrees. The mixture is heated for two hours and then extracted with naphtha. The naphtha extract is washed with water. 2 grams of activated carbon are added and then filtered off. More naphtha is added (eg. 75 mL. per 10 grams). The mixture is chilled (0 degrees C.) yields 40-50% oleamide. Pure oleamide can be obtained by repeated crystallizations from ethanol (30-40% yield).

Reference: Roe 1949

Oleic acid occurs in olive oil. See page 118. Urea occurs in urine.

The Reactions Used

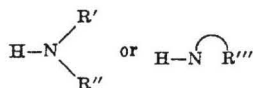
By Takashi Seki

Osaka Japan

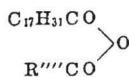
March 22, 1967

For example, (1) an octadecadienoic acid is made to react directly with an amine of the formula:

(wherein R', R'' and R''' are as defined above) in the presence or absence of such dehydrating agent as a di-substituted carbodiimide compound, *p*-toluenesulfonic acid or *p*-toluene-sul-



fonyl chloride in an aqueous or organic solvent, (2) an octadecadienoic acid is converted to acid chloride (*Organic Synthesis* vol. 37, page 56) and the resulting acid chloride is brought into contact with at least an equimolar amount of the amine in the presence of a basic condensing agent, (3) a lower alkyl ester of an octadecadienoic acid is made to react directly with the amine in the presence or absence of a solvent and condensing agent (this method is the di-substituted one called "aminolysis method") or (4) a mixed acid anhydride of an octadecadienoic acid of the formula:



(wherein R''' is an alkyl or halalkyl radical having one to 20 carbon atoms) is made to react with the amine in the presence of a basic condensing catalyst. Source: Seki 1971

N-Substituted Amides of Natural Fatty Acids

By Takashi Seki

Osaka Japan

April 23, 1965

Though the reaction temperature, of course, generally depends on the employed solvent, it is within a temperature range of from -20° C. to near the boiling point of the solvent. The reaction is preferably carried on in an atmosphere of such an inactive gas as nitrogen, helium and the like. Thus, the amide derivatives of the objective products are obtained under relatively mild conditions in high yields and simplicity without oxidation of the reactant.

In case of the direct reaction of the natural oil or lower alkyl ester of natural fatty acid and the amine the reaction method for producing the amide derivatives is as follows: That is, about 1 mol of the said oils and 1 to 100 equivalent mols of the said amines are mixed in the absence or presence of solvents such alcohols as methanol, ethanol or the like, such aromatic hydrocarbons as benzene, toluene, xylene or the like, such halogenoalkanes as methylene chloride, chloroform, carbon tetrachloride or the like, and such alkenes or alkanes as petroleum ether, benzene, gasoline, ligroin or cyclohexane, such ethers as tetrahydrofuran, dioxane and the like, or a mixture thereof, and the mixture is subjected to the reaction in the absence or presence of catalyst amount or equimolar amount to the amine of an auxiliary agent of condensation, such as alkoholate of alkali metal, i.e. lithium, methylate, lithium ethylate, sodium methylate, sodium ethylate, potassium-*t*-butylate and the like, or acidic auxiliary agents, i.e. *p*-toluenesulfonic acid and the like, thereby to yield the amide derivatives. In this reaction, a formal alcohol may be removed from the reaction system.

It is a matter of course that even absence of any solvents and any auxiliary agents can sufficiently accomplish the purpose.

In case of using amines having lower boiling point, if necessary, an autoclave may be employed but in case of another amines the reaction mixture is stirred under atmospheric pressure while being heated at need, thereby easily to yield the objective amide.

In carrying out the reaction, a mixture of respective substance is stirred at a suitable temperature of between, room temperature and 400° C. for about 3 hours to a month.

If necessary, the reaction is carried on in an atmosphere of an inactive gas such as nitrogen, helium and the like to prevent from producing undesirable byproducts and coloring, thereby to yield the

objective product, which is, at need, subjected to a fractional distillation, recrystallization using a petroleum hydrocarbon, acetone or the like or urea method to remove saturated fatty acid amides. If alkali alcoholate is used as an auxiliary agent, conjugated double bond isomer are partially obtained. However, the present invention confirmed that saturated and isomerized fatty acid amides affect on the human body no undesirable effect.

Preparation of N-Methyl Linseed Oil Fatty Acid Amide

Ten grams of linseed oil and 10 g. of methylamine are stirred in an autoclave at room temperature for 240 hours.

After the reaction is over, the reaction mixture is poured into a mixture of 1 N hydrochloric acid and ice, and subjected to extraction with ethyl ether.

The ether layer is washed successively with 5% hydrochloric acid, 5% sodium carbonate aqueous solution and water, and then dried over sodium sulfate. Upon evaporation of ether, the residue is subjected to fractional distillation in vacuo, thereby to yield 8.9 g. of N-methyl linseed oil fatty acid amide, B.P. 178-190° C./0.03 mm. Hg, I.R. 1,650 cm.-1. (I.R. means wave number of the infrared absorption spectrum.)

Preparation of N-Cyclohexyl Linseed Oil Fatty Acid Amide

Twenty grams of linseed oil and 10 g. of cyclohexylamine are stirred in an atmosphere of nitrogen for 70 hours at a temperature of 145° C. to 150° C. while being heated. After the reaction is over, the reaction mixture is poured into a mixture of 1 N hydrochloric acid and ice, and subjected to extraction with ethyl ether. The ether layer is washed successively with 5% hydrochloric acid, 5% sodium carbonate aqueous solution and water, and dried over anhydrous sodium sulfate.

Upon evaporation of ethyl ether, the residue is subjected to careful fractional distillation, thereby to yield 18.2 g. of N-cyclohexyl linseed oil fatty acid amide, B.P. 195-208° C./0.03 mm. Hg.

Source: Seki 1970

Preparation of Lauric Diethanolamide from Lauroyl Chloride

by Irving Joseph Krems of Bronx, N.Y.
and Henry Arnold Goldsmith of Long Island, NY
December 28, 1950

Part A.—About 202 grams (1 mol) of melted lauric acid (90%) was mixed with about 35 mL. (0.4 mol) of phosphorus trichloride at a temperature of approximately 40° C. After the resultant mixture had separated into two immiscible liquid layers, the lower layer consisting essentially of phosphorous acid was separated from the lauroyl chloride present in the upper layer.

Part 3.—A mixture containing approximately 116.5 grams (1.1 mol) of diethanolamine dissolved in about 200 mL. of water and about 100 mL. of ethylene dichloride was placed in a reaction vessel and cooled to a temperature of about 10° to 20° C. Lauroyl chloride, prepared in the manner described in Part A' was slowly added, with stirring until the pH of the resulting solution had dropped to about 8.5, e. g., after about 110 grams of lauroyl chloride had been added. Thereafter, about 61 grams (0.95 mol) of potassium hydroxide (87.5%) dissolved in about 200 mL. of water and about 110 grams of lauroyl chloride were introduced, the temperature being maintained between 10° to 20° C. and the pH around 8.5 to 9. The total amount of lauroyl chloride introduced into the mixture was 220 grams (1 mol). Upon heating to a temperature of approximately 70° to 75° C. the mixture thus prepared separated into two immiscible liquid layers.

Part C.—The upper organic layer was removed and diluted with about 100 mL. of chlorinated solvent and azeotropically distilled until substantially all water had been removed. The cooled anhydrous solution was then filtered to remove precipitated salts and soaps after which the clear filtrate was distilled, the last traces of solvent being removed under reduced pressures, e. g., about 10 mm. mercury and at a temperature not exceeding 100° C. The pale liquid residue crystallized to a low-melting waxy material containing about 96% lauric diethanolamide, about 3% lauric acid, and about 1% diethanolamine ester.
Source: Krems 1954

Preparation of Cocoa Fatty Acid Amide Using the Aminolysis Method

by Ernst Alfred Mauersberger

Maarssen, Netherlands October 15, 1937

450 grams of cocoa fatty acid and 120 ccm. of monoethanolamine are vigorously stirred together resulting in the production of a soap-like solid body, which is then heated to 220° C., in an autoclave causing the pressure in the latter to rise to about 120 pounds. The liberated water of reaction is blown off. The reaction product is a hard, wax-like amide, Pure white in color, which slowly turns brown in the air.

Source: Mauersberger 1939

See: **Vandevoorde, S. et al.** Modifications of the Ethanolamine Head in N-Palmitoylethanolamine: Synthesis and Evaluation of New Agents Interfering with the Metabolism of Anandamide.; *J Med Chem.* (2003) 46(8):1440-8
Lambert D.M, et al; The Palmitoylethanolamide Family: a New Class of Anti-inflammatory Agents?; *Curr Med Chem.* (2002) (6):663-74.

Industrial Manufacture of Fatty Acid Ethanolamides

by Chemische Werke Huls Aktiengesellschaft

Marl, Germany June 13, 1972

The manufacture of fatty acid ethanolamides can start from a fatty acid or from the ester, acid chloride or acid anhydride, which is reacted with a monoethanolamine or diethanolamine. Industrially, fatty acids or fatty acid esters are exclusively used. In general, the procedure followed is to take one component and add the other component dropwise. Thereafter the mixture is heated to 130 to 180° and one mol of water or if using the fatty acid ester, one mole of alcohol is driven off per mol of acid.

Lauric Acid Monoethanolamide Preparation

856 g of lauric acid methyl ester (4 mols) were treated, in a three-neck flask with stirrer, reflux condenser and thermometer, with 15 mL. of an 11.7 per cent strength solution of sodium methylate in methanol, and 122 g (2 mols) of monoethanolamine were then added at 70° C. The reaction temperature was then gradually raised to 100° C and kept thereat until approx. 70 mL. of methanol had evaporated off. This took about

6 hours. Thereafter the mixture was stirred for a further 10 hours at 130 to 140°C. After a further addition of 122 g (2 mols) of monoethanolamine the mixture was again stirred for 4 hours at 140°C, in the course of which no further methanol was formed.

The reaction product had the following composition:

Lauric acid monoethanolamide	99.0 %
Lauric acid aminoethyl-ester	<0.1 %
NO-dilauroylethanolamide-ester	< 0.5 %
Monoethanolamine	0.3 %
Fatty acid bonded as a salt, and free fatty acid	0.3 %
Iodine colour number (fused)	2-4
No amine odour	

Preparation of Oleic Acid Monoethanolamide

17,350 g of oleic acid (61.5 mols), 1,880 g of monoethanolamine (30.8 mols) and 500- mL. of 11.7 per cent strength sodium methylate solution were heated to 150-160°C in a stirred vessel of 40 L. capacity and 1,400 of water and methanol (from the catalyst solution) were collected whilst passing a weak stream of nitrogen into the mixture. After 8 hours, a further 1,880 g of monoethanolamine (30.8 mols) were added and the mixture was again heated for a further 8 hours at 150—160°C.

The reaction product was (as an oleic acid derivative) very light-coloured and consisted of:

Oleic acid monoethanolamide	96.0 %
Oleic acid aminoethyl-ester	<1 %
ON-dioleylethanolamide-ester	< 1 %
Monoethanolamine	0.8 %
Fatty acid bonded as a salt	2.8 %
Iodine colour number (fused)	20—30
No amine odour	

Source: Chemische Werke Huls Aktiengesellschaft 1975

Purification of Fatty Acid Amides Using Urea

by Sumitomo Chemical Co.

Osaka, Japan

January 3, 1966

The natural fatty acid amides are mixtures of saturated fatty acid amides and unsaturated fatty acid amides. The present invention is based on the fact that the unsaturated fatty acid amides can be isolated very easily from a mixture of fatty acid amides by treating the fatty acid amides with urea or thiourea. The unsaturated fatty acid amides have more effective biological activity.

The following is illustrative of the process of the present invention. To one part by weight of an acid amide mixture, there are added simultaneously with vigorous stirring at a temperature between room temperature and 100°C 0.1 to 10 parts by weight of urea or thiourea, dissolved in water, methanol or ethanol. The stirring, if necessary, with the heating is continued until the resulting reaction mixture becomes almost transparent. The mixture is allowed to cool overnight at room temperature, whereafter the precipitated crystals are removed by filtration, and the filtrate is treated with an equal amount of water to separate the oil, which is extracted with ether, washed with water, dried and concentrated.

To 10 parts by weight of hot cyclohexyl amides of fatty acids of safflower oil (iodine value, 90), is added a hot solution of 5 parts of urea in 10 parts of methanol, simultaneously with vigorous stirring and the mixture is allowed to stand at room temperature for 24 hours. After the separated crystals are removed by filtration, the filtrate is treated with water and extracted with ether. The extract is washed with water, dried and concentrated to give the objective material having an iodine value of 140. Source: Sumitomo Chemical Co. 1967

Preparation of Olive Oil and Coconut Oil Ethanolamides

by I.G. Farbenindustrie Aktiengesellschaft

Frankfort-on-Main, Germany

June 4, 1931

200 parts by weight of olive oil or 140 parts by weight of coconut oil are heated under reflux with 50 parts by weight of 20 ethanolamine for several hours to a temperature of 100-140° C. The crude, light yellow reaction product, which is solid at room temperature, dissolves readily in organic solvents, such as benzene.

Source: I.G. Farbenindustrie Aktiengesellschaft 1932

Preparation of Fatty Acids

Isolation of Linoleic Acid

By Takashi Seki

Osaka Japan

March 22, 1967

Comparatively pure linoleic acid can be obtained, for example, by the purification of safflower oil fatty acid such as low temperature recrystallization method, distillation method, urea method, salt recrystallization method, etc. Source: Seki 1971

Isolation of Oleic Acid from Olive Oil

An acetone solution of saponified olive oil is chilled to -20° to crystallize saturated acids. At -60° oleic acid crystallizes.

Production of Monoalkylamines

by Carl T. Kautter of Berkeley, California

October 1, 1934

The reaction was effected in a suitable pressure reaction vessel having a capacity of about 6.2 liters and equipped with a thermometer, pressure gauge, expansion valve and an inlet tube by means of which the reactants could be introduced into the lower portion of said reaction vessel.

The reaction vessel was charged with about 6 liters of an aqueous ammonia solution having a concentration of about 170 gm. NH_3 per liter (18.31%). 88 gm. (2.0 moles) of ethylene oxide were added at a temperature of about 20°C . and the vessel was closed, immersed in a steam bath and heated at 94°C . for one hour. The maximum gauge pressure was 36 lbs./sq. in. At the end of this time the excess ammonia was expanded from the reaction vessel and absorbed in water. The reaction mixture was discharged from the reaction vessel and the monoalkylamine was recovered therefrom by distillation.

The molal ratio of ethylene oxide: ammonia: water in the reaction mixture was 1:30:129.

The monoethanolamine was obtained in a yield of 83.2%.

Source: Kautter 1936

Chapter 1: Coca, The Source of Cocaine

by W.E. Stafford

The most important stimulant of the ancient Peruvians was *Erythroxylon Coca*. Specimens of its 3-ribbed leaves were found by the writer in many prehistoric graves along the Peruvian coast, usually in bags suspended from the necks of mummies, or in bundles wrapped in cloth. Some of the coca bags, or pouches, were wroven in beautiful and intricate designs, often representing conventional figures of birds, mammals, or fishes. All were accompanied by small gourds (a variety of *Cucurbita lagenaria*) containing lime, and a spatula by means of which the lime was dipped out. In place of lime, woodashes were sometimes used. The use of lime or ashes to set free the alkaloid contained in the leaves recalls the same custom in connection with the betel of Asia, the piptadenia snuff..., and the "green tobacco" of the Mexicans. That its efficacy should have been independently discovered by the primitive inhabitants of such widely separated regions is remarkable. The lime



POUCH CONTAINING COCA LEAVES FROM PREHISTORIC PERUVIAN GRAVE, TOGETHER WITH GOURD CONTAINING LIME.

gourds were not infrequently ornamented, and in those discovered in some localities, especially at Africa, on the coast of northern Chile, the spatulae were of carved bone, many of them of beautiful designs, and the gourds were suspended by carved bone toggles resembling Japanese netsukes. Specimens of the latter may be seen in the Field Museum at Chicago. Two packages of leaves from Peruvian graves sent to the Smithsonian Institution by the late Henry Meigs, the builder of the great trans-Andine railway from Callao to Oroya, we found by the writer, one bearing the label "tobacco," the other "Paraguay tea." The contents of both of these packages proved to be coca leaves, easily identified by the pseudo-rib, extending on each side of the midrib from the base to the apex.

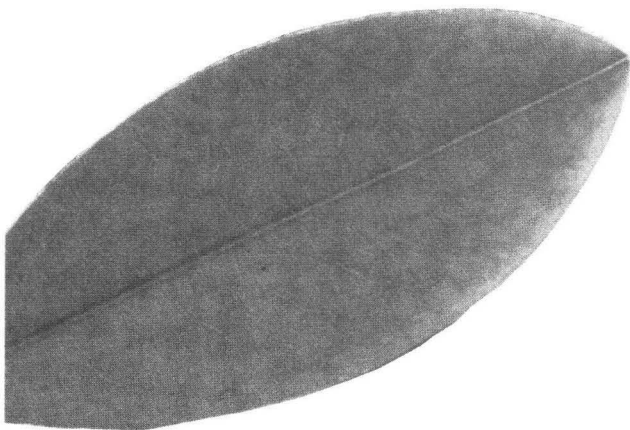
In the accompanying illustrations... is a photograph by Mr. Grover Bruce Gilbert of a specimen collected by Mr. O.F. Cook at Santa Ana, Peru, during his recent mission to South America (1).

The leaves of *Erythroxylon Coca*, which from remote ages have been used by South American Indians as a stimulant, are the source of cocaine, now so widely used in surgery to deaden pain and also as a narcotic. Like other narcotic alkaloids, although it is a great blessing to the human race when wisely used, yet when abused it is a terrible curse. In Peru the use of coca by miners and cargueros is still common. There the entire leaf is used. In North Brazil, where it is also extensively used under the name *ipadú*, the leaves are ground to a fine powder. Spruce, who saw the process of preparing the leaves near the mouth of the Rio Negro in 1851, gives the following account of it in Hooker's *Journal of Botany* for July, 1863:

The leaves of *ipadú* are pulled off the branches one by one and roasted on the mandiocca-oven, then pounded in a cylindrical mortar, 5 or 6 feet in height, made of the lower part of the trunk of the Pupunha or Peach Palm (*Guilielma speciosa*), the hard root forming the base and the soft inside being scooped out. It is made of this excessive length because of the impalpable nature of the powder, which would otherwise fly up and choke the operator; and it is buried a sufficient depth in the ground to allow of its being easily worked. The pestle is of proportionate length and is made of any hard wood. When the leaves are sufficiently pounded the powder is taken out with a small cúa fastened to the end of an arrow. A small quantity of tapioca, in powder, is mixed with it to give it consistency, and it is usual to add pounded ashes of *Imba-úba* or Drum tree (*Cecropia peltata*), which are saline and antiseptic. With a chew of *ipadú* in his cheek, renewed at intervals of a few hours, an Indian will go for days without food and sleep.

In April, 1862, I assisted, much against my will, at an Indian feast in a little rocky island at the foot of the falls of the Rio Negro; for I had gone down the falls to have three or four days' herborising, and I found my host—the pilot of the cataracts—engaged in the festivities, which neither he nor my man would leave until the last drop of cauim (coarse cane or plantain spirit) was consumed. During the two days the feast lasted I was nearly famished, for, although there was food, nobody would cook it, and the guests sustained themselves entirely on cauim and *ipadú*. At short intervals *ipadú* was handed around in a large calabash with a tablespoon for each to help himself, the customary dose being a couple of spoonfuls. After each dose they passed some minutes without opening their mouths, adjusting the *ipadú* in the recesses of their cheeks and inhaling its delightful influences. I could scarcely resist laughing at their swollen cheeks and grave looks during these intervals of silence, which, however, had two or three times the excellent effect of checking an incipient quarrel. The *ipadú* is not sucked, but allowed to find its way insensibly into the stomach along with the saliva. I tried a spoonful twice, but it had little effect on me and assuredly did not render me insensible to the calls of hunger, although it did in some measure to those of sleep. It had very little of either smell or taste, and in both reminded me of weak tincture of henbane. I could never make out that the habitual use of *ipadú* had any ill results on the Rio Negro; but in Peru its excessive use is said to seriously injure the coats of the stomach, an effect probably owing to the lime taken along with it.

1) See Mr. Cook's paper entitled "Staircase Farms of the Ancients" in *The National Geographic Magazine*, 29: 474-534. May, 1916.
Source: Stafford 1916



Coca

by Horatio C. Wood, Jr. M.D.

Charles H. LaWall, Ph.M., D.Sc., Phar.D.

Heber W. Youngken, Ph.M., Ph.D.

John F. Anderson, M.D

Ivor Griffith, Ph.M

Coca. Cocoe Folia *U.S.P.* VIII. *Br.* 1898. Coca Leaves. Cuca. Feuilles de Coca, *Fr.* Cocablätter, *G.* Coca del Peru, Ipadú, *Sp.*—

“The dried leaves of *Erythroxylum Coca* Lamarck (Fam. *Erythroxylaceae*), known commercially as Huanuco Coca, or of *E. Truxillense* Rusby, known commercially as Truxillo Coca, yielding when assayed by the process given below, not less than 0.5 per cent. of the ether-soluble alkaloids of Coca. “*U.S.* VIII.” The dried leaves of *Erythroxylum coca*, Lam., and its varieties.” *Br.*, 1898.

The coca plants are shrubs or small trees, some of the species reaching the height of fifteen or twenty feet. It is conjectured that the original habitat was in the Peruvian mountains, from 7° South to 10° North, but either spontaneously or through cultivation the coca shrubs have spread until they are found in the whole Eastern curve of the Andes, from the Straits of Magellan to the borders of the Caribbean Sea, growing on the moist sides of the mountains at the elevation of 1500 to 6000 feet, the climatic requisites being moisture and equable temperature, with a mean of about 17.7° C. The wild coca shrub commonly reaches the height of 12 feet, and some are 18 feet, but the cultivated coca is usually kept down to about 6 feet. The leaves are gathered three times a year; the first harvest, or preliminary picking, is taken at the time of the trimming of the bushes, from the cut-off twigs. Then about the end of June, a scanty crop is gathered, while the last crop of the season is gathered in October or November. Harvesting must always take place in dry weather, so that the fresh leaves when spread out in layers two or three inches thick on the drying pavement can be collected in six or eight hours.

The coca plant, which is propagated from the seed in nurseries, begins to yield in eighteen months, and continues productive for half a century. The leaves, when mature, are carefully picked by hand so as to avoid breaking them or injuring the young buds, are slowly dried in the

sun, and are then packed in bags holding from twenty-five to one hundred and fifty pounds each. Coca was in general use among the natives of Peru at the time of the conquest, and has continued to be much employed to the present time. It is affirmed that nearly ten million dollars worth, or forty million pounds, are annually produced, some plantations yielding three or four harvests a year. For details as to method of cultivation, etc., see *T. G.*, Jan., 1886; also *C. D.*, 1897, 182. Coca leaves are chiefly imported from Peru, where the plant has been under cultivation since prehistoric time. Two varieties of the coca leaf occur in the commerce of the United States, namely, the so-called Huanuco coca and the Truxillo coca, the Huanuco variety being produced in Bolivia, Huanuco, Brazil, Venezuela and Argentina, while the Truxillo coca is produced chiefly in Northern Peru. The great variation in the leaves and other portions of the coca plant, produced by its long-continued cultivation, has produced much doubt and discussion as to the specificity and characteristics of the plant: H.H. Rusby has made an elaborate study of the subject (*D. C.*, Nov., 1900).

Huanuco coca has been for a long time believed to be obtained from *Erythroxylum Coca*, this belief is confirmed by Rusby and was accepted by the Pharmacopoeial authorities.

Truxillo coca is the product of the *E. Coca Spruceanum* of Burck; the name "*spruceanum*" had, however, been used elsewhere before it was suggested by Burck and in obedience to the ordinary rules of botanical nomenclature it was changed by Rusby, who regards it as a distinct species, to *E. Truxillense*.

Coca is cultivated in the British East and West Indies, and in Java, and the product is said to appear, in the London markets, under the names of Truxillo coca and Java coca. This coca is entirely distinct from the Truxillo coca of the American market, and does not reach the United States. According to Emma Reens, *E. spruceanum* or novogranatense are cultivated in Java (*B. Soc. Pharm.*, 1919, xxvi, 497). The coca shrubs of India and Ceylon are the offspring of plants originally sent out from Kew Gardens, which plants were derived from seeds obtained in Huanuco, and were considered by Morris as representing a variety of *E. Coca* to which he gave the name of Nova-Garatense. According to Rusby, however, this plant is a distinct species, and the same as that previously described by Jacquin, from Colombia, under the name of *E. carthagenense* (the name carthagenense not being, as it is held in the Kew Index, a synonym of *E. areolatum*).

The leaves of the different varieties of coca do not, on the whole, resemble one another at all closely, but are distinguished from most other

leaves by a slightly curved line on each side of the midrib, running from the base to the apex. This line has the appearance of a rib, but is really not of this character, having been produced during development by the peculiar folding of the leaf in the bud. The two commercial varieties were very well described in the *U.S.* VIII as follows:

“Huanuco Coca.—Greenish-brown to clear brown, smooth and slightly glossy, thickish and slightly coriaceous, stoutly and very shortly petioled; blade 2.5 to 7.5 Cm. long and nearly elliptical, with a very short and abruptly narrowed basal portion and a short point, the margin entire; midrib marked above by a slight ridge, very prominent underneath, the remaining venation rather obscure, especially above, underneath, a conspicuous line of collenchyma tissue runs longitudinally on either side of the midrib and about one-third of the distance between it and the margin, the enclosed areola being of a slightly different color from the adjacent surface, odor characteristic, taste bitterish, faintly aromatic, followed by a numbness of the tongue, lips and fauces.

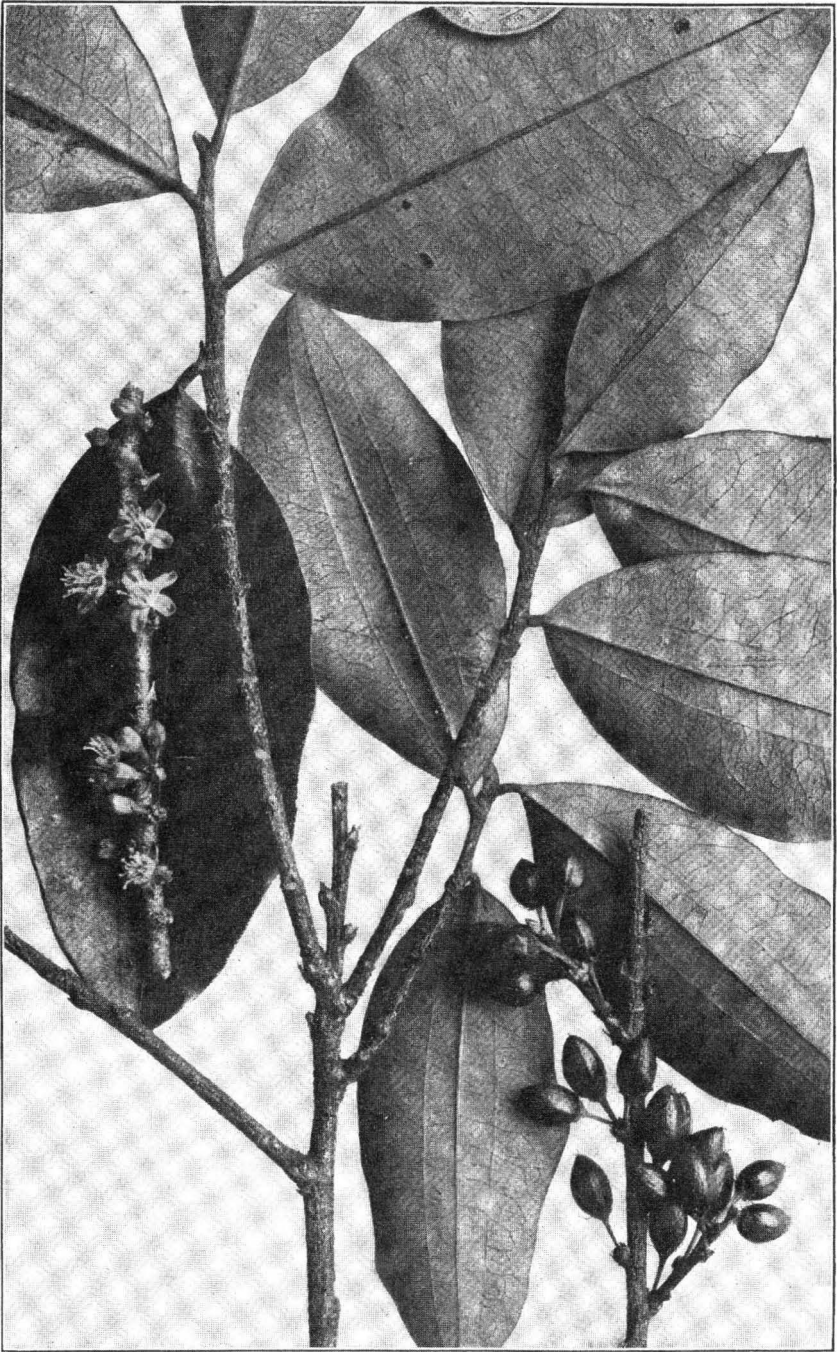
“Truxillo Coca.—Pale green, thin, brittle and usually much broken, smooth, but not shining, shortly and stoutly petioled; blade 1.6 to 5 Cm. long and one-third to one-half as broad, obovate to oblanceolate, narrowed from near the middle into the petiole, usually with a slight projecting point at the summit, the margin entire; underneath two irregular lines of collenchyma tissue, usually incomplete or obscure, and frequently wanting, run beside the midrib at about one-third the distance from it to the margin; odor more tea-like than that of Huanuco Coca; taste and numbing effect similar.” *U.S.* VIII. “The midrib itself is prolonged into a minute horny apiculus, which, however, is frequently broken off. Most of the epidermal cells of the under surface are seen in transverse section to project in the form of small papillae.” *Br.*, 1898.

In South America many of the Indians habitually chew the leaf of the coca plant, generally mixed with some alkali as ashes or lime. It is stated on good authority that they will go for days performing hard physical labor without any other food. It is, however, clearly proven that these leaves do not take the place of nutriment, but simply put off the sense of fatigue and hunger. Eventually, however, this habit undermines the health and finally the inveterate excessive cocachewer can be recognized by his uncertain step, general apathy, sunken eyes surrounded by deep purple aureoles, trembling lips, green and crusted teeth, and excessively fetid breath, with peculiar blackness about the corners of the mouth. An incurable insomnia is apt to be developed, emaciation becomes extreme, dropsy appears, and even death results from a condition of general marasmus. It has been believed that the effects of coca chewing are

different from those produced by the alkaloid cocaine and hence it has been by some argued that the coca leaf contains other active principles, but there is no difference between the results of the habit as practiced by the South American Indian and the use of the alkaloid by depraved Caucasians, which cannot be readily explained on the ground of difference in the mode of taking the stimulant or racial variation. While there are other active substances present in the coca leaf, it is not manifest that they modify the action of the crude drug materially.

Coca has a slight bitter tonic effect as well as a stimulant action upon the central nervous system and has been used as a tonic in neurasthenia and other debilitated conditions. The danger of the formation of the habit, however, far outweighs any value the drug may possess, and the use of the crude preparation of coca seems to us hardly justifiable except under the most extraordinary conditions. The *U.S. VIII*, recognized a fluidextract, the dose of which was from thirty to sixty minims (2-3.9 cc.), and a wine the dose of which was two to eight fluidrachms (7.5 to 30 cc.). Source: Wood 1926

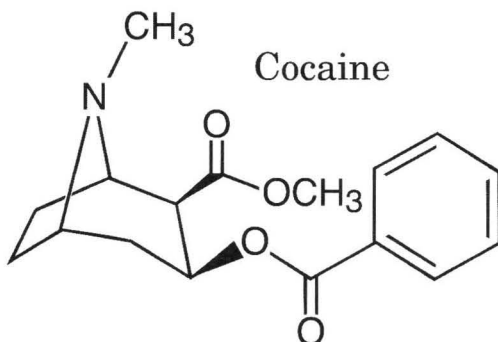




ERYTHROXYLON COCA, THE SOURCE OF COCAINE. PHOTOGRAPH OF SPECIMEN COLLECTED AT SANTA ANA, PERU, BY O. F. COOK.

Chapter 2: Cocaine

(Benzoyl methyl ecgonine) $C_{17}H_{21}O_4N$. M.W. 303

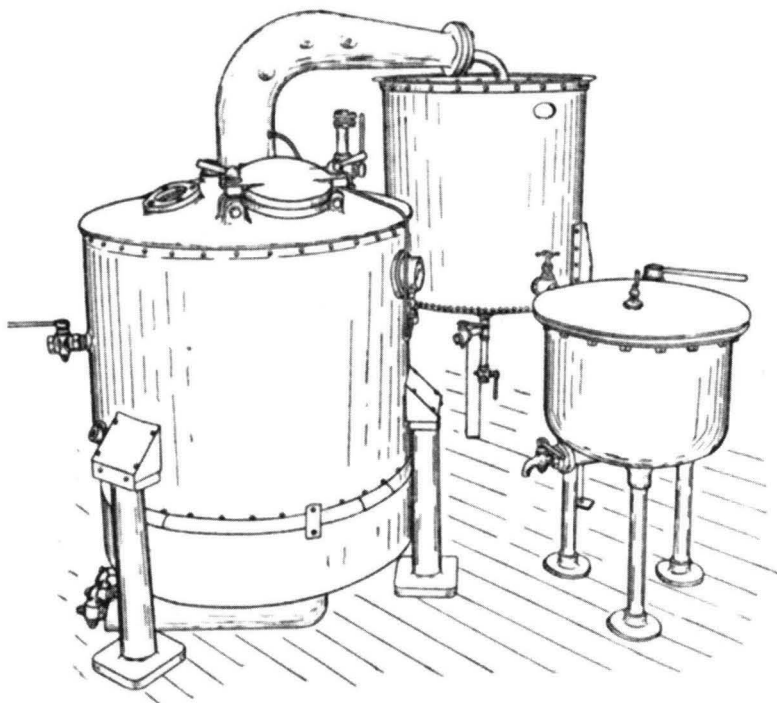


by M. Barrowcliff, M.B.E., F.I.C. and
Francis H. Carr, C.B.E., F.I.C.

Cocaine is obtained from the leaves of various species of *Erythroxylon*. Three kinds of coca leaves occur in commerce: (I) *Erythroxylon Coca*, Lamarck, Huanuco or Bolivian Coca; (II) *E. Truxillense*, Rusby, Truxillo or Peruvian Coca, also cultivated in Ceylon; (III) *E. Spruceanum*, Burck, Java Coca. In addition to the foregoing species, many varieties of *Erythroxylon* exist, a few of them only containing significant proportions of cocaine. The percentage of alkaloids present in commercial coca leaves varies from 0.6 to 0.4, Java leaves containing the highest amount. Associated with cocaine are a number of other alkaloids: cinnamyl-cocaine, the chief constituent of the Java leaves; a- and b-truxilline, cocamine or isatropyl-cocaine, and benzoyl-ecgonine, which possess, with cocaine, the common property of affording ecgonine on hydrolysis, together with benzoic, cinnamic, or truxillic acids. Tropacocaine, another important constituent, when hydrolysed, gives pseudo-tropine, a stereo-isomeride of tropine, and benzoic acid. Ecgonine can be converted into cocaine, by methods to be described; pseudotropine cannot.

Crude Cocaine.—In order to save freight and to eliminate the risk of deterioration to which the leaves are subject, the alkaloids are commonly, though not always, extracted in the country of origin, and imported into Europe under the name of “crude” cocaine, which may consist either of the bases themselves, or of their hydrochlorides. “Crude” cocaine, from South America, is an extremely variable article and frequently is heavily adulterated. Purchase on assay even is attended by risk, as the same keg may contain material of greatly varying purity.

The preparation of crude cocaine is believed to be carried out in South America by extracting the finely ground leaves with dilute sulphuric acid. The acid extract is made alkaline with sodium carbonate and the liberated alkaloids are dissolved in petroleum. From this they are re-extracted into dilute sulphuric acid and reprecipitated with soda, the precipitate being washed with water, pressed, and dried. (*C. and D.* 1912, 80, 51.) Java cocaine, from which a very large proportion of the world's supply of pure cocaine is now obtained, is manufactured as follows: the leaves are dried in a well-ventilated but cool place and, after powdering in a disintegrator, are mixed with from 3 to 5 % of slaked lime and sufficient water to afford a stiff paste. The mixture is placed in a jacketed iron vessel provided with good stirring facilities and is extracted, at a temperature of 80° - 100° , with a petroleum fraction distilling at 200° - 250° ; or, in the cold, with benzene or solvent naphtha. The oil solution after separation is agitated with dilute hydrochloric acid, sufficient in amount to extract the bases in the form of their hydrochlorides. The aqueous solution is then either neutralised and evaporated down, the salts being crystallised out, or is treated with sodium carbonate, whereby the crude cocaine alkaloids are precipitated.



Vacuum Still for Methyl-ecgonine.

Pure Cocaine.—Although it is possible to purify cocaine by crystallisation of the hydrochlorides of the mixed alkaloids, this procedure has been found to be tedious and uneconomic; the proportions of the associated alkaloids vary considerably, and Java cocaine, as has already been stated, consists mainly of the cinnamyl derivative. The technical method of manufacture consists of hydrolysing the alkaloids to methyl ecgonine, or to ecgonine, and reconverting the purified methyl-ecgonine or ecgonine into cocaine by benzylation, or esterification and benzylation respectively. Hydrolysis to methyl-ecgonine may be effected by boiling with hydrochloric acid in methyl alcohol under a reflux condenser. For complete hydrolysis the hydrochlorides of the alkaloids are dissolved in water, the solution is made acid with hydrochloric acid to the extent of about 0.2% and heated for one hour in an enamelled or silver-lined autoclave to 150°, whereby the methyl group, as well as the benzoyl, cinnamyl, truxillyl, etc., radicles are split off. The resulting solution is filtered, after cooling, from the liberated acids and evaporated to dryness. Ecgonine hydrochloride is thus obtained, associated at times with some pseudotropine hydrochloride. It is washed with alcohol or acetone and the base isolated by treatment with sodium carbonate and extraction, after drying, with hot alcohol. It is purified by crystallisation from the same solvent, from which it separates in colourless prisms, containing 1 molecule of water, and melting at 198°, or by crystallisation of its barium salt.

Methylation.—The pure ecgonine is converted into its methyl ester, by heating with methyl alcohol and hydrochloric or sulphuric acid, or by employing sodium methyl sulphate, and the ester, after liberation from its salt, is extracted with chloroform and cleaned by distillation in a high vacuum.

Benzylation.—Distilled methyl-ecgonine dissolved in benzene is mixed with a small excess of benzoyl chloride, and the mixture heated at its boiling point under a reflux condenser. The cocaine hydrochloride obtained on cooling is converted to base and is purified by recrystallisation from alcohol. The hydrochloride is then re-formed and recrystallised from mixtures of alcohol and light petroleum or ether. Recrystallisation must be repeated, if necessary, until the pharmacopoeial tests of purity are complied with, since associated impurities are apt to possess dangerous toxic properties.

Several other methods have been proposed for the conversion of ecgonine into cocaine:—ecgonine is benzylated by heating with benzoic anhydride or benzoyl chloride, or by heating the hydrochloride with benzoyl chloride, and the resulting benzoyl ecgonine esterified by

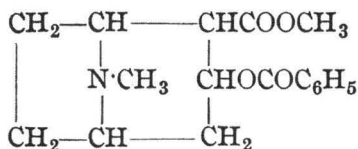
boiling with methyl iodide and one molecular proportion of sodium in methyl alcohol solution. (Liebermann and Giesel, *Ber.* 1888, 21, 3196), (*D.R.P.* 46702.) The conversion is carried out in one operation, whereby ecgonine is heated together with methyl iodide and benzoic anhydride under pressure. (Merck, *Ber.* 1885, 18, 2953.)

The hydrolysis of crude cocaine to ecgonine has been carried out by boiling with an excess of hydrochloric acid (sp.gr. 1.1-1.2) (*D.R.P.* 46702), and by boiling for an hour with 60 times its weight of 7% hydrochloric acid (Greshoff, *Pharm. Weckbl.* 1907, 44, 961). De Jong, criticising the latter procedure, has stated that under these conditions decomposition results. (*Chem. Weckbl.* 1907, 5, 645.)

Tests: A solution of 0.1 gram in 5 c.c. of water, acidified with 3 drops of dilute sulphuric acid (10% w/w) is mixed with 3 drops of decinormal potassium permanganate solution, when the colour should not disappear in half an hour (*U.S.P.*). For this test to be complied with it is necessary that every trace of organic solvent should have been removed

A solution of 0.1 gram of cocaine hydrochloride in 80 c.c. of water is treated carefully, without shaking, with 2 c.c. of a mixture of 9 volumes of water and 1 volume of 10% ammonia solution; no turbidity should form within one hour. On then scratching the sides of the vessel with a glass rod a crystalline precipitate (cocaine) should be thrown down, the supernatant liquor remaining clear.

Cocaine hydrochloride should melt at 180°-186° (B.P.), 183° (P.G.), 186° (*Fr. Codex*). It should be perfectly colour-less, and should afford a bright, neutral solution in water. This salt of cocaine is the one most generally employed in medicine. It is largely used for producing local anesthesia in minor operations and in dental practice. Given internally, or in small hypodermic doses, it acts as a nerve stimulant, restorative, and tonic. The mental exhilaration it produces often conduces to the formation of the "cocaine habit," which is even more unfortunate than the "morphia habit" in its results. Source: Barrowcliff 1920

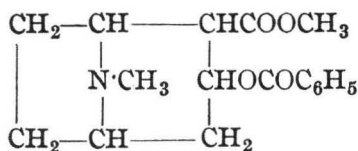


COCAINA. U.S., Br. COCAIN Cocain.

"An alkaloid [C₁₇H₂₁O₄N] obtained from the leaves of *Erythroxylon Coca* Lamarck and other species of *Erythroxylon* (Fam. *Erythroxylaceae*)." U.S. "Cocaine, C₁₇H₂₁O₄N, is an alkaloid obtained from the leaves of *Erythroxylon Coca*, Lam., and its varieties." Br.

Benzoyl-ecgonine-methyl-ester: Benzol-methyl-ecgonine; Cocainum Cocaine, *Fr. Cod.*; Cocain, Kokain, *G.*

Squibb's process for cocaine and its hydrochloride is as follows: Coarsely ground coca leaves are repercolated with an aqueous five per cent. solution of sulphuric acid, and a very dense, slightly acid percolate is obtained; this is thoroughly agitated with pure coal oil and an



excess of sodium carbonate; the liberated alkaloid is retained by the coal oil, and is nearly free from coloring matter; the oily solution is then agitated with acidulated water, and again precipitated by sodium carbonate in the presence of ether. The ethereal solution of cocaine is treated with diluted hydrochloric acid fractionally, and the nearly colorless solutions of cocaine hydrochloride are cautiously evaporated in shallow porcelain pans almost to dryness. The product is in the form of a white, crystalline, granular powder, and is a nearly pure anhydrous salt. (*Ephem.*, 1887, 906.) For Henrique's process see *Proc. A. Ph.* 4., 1895, 999.

Owing to the small yield, it is found more profitable to manufacture cocaine in South America and export it, thus saving the expense of transporting the bulky coca leaves.

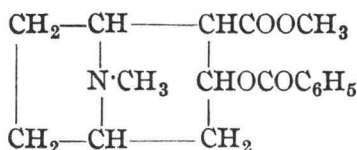
The cocas contain a number of alkaloids which Henry (*Plant Alkaloids*, 1924, p. 95) divides into four groups; (1) the cocaines, (2) pseudotropeines, (3) acylecgonines, (4) hygrines. In the first group is cocaine (methyl benzoyl ecgonine), cinnamyl-cocaine (methyl-cinnamoylecgonine), and alpha- and beta-truxilline, C₃₈H₄₈O₈N₂. Alphatruxilline is also known as cocamine and isotropyl-cocaine.

The second group comprises one alkaloid, tropacocaine, which is a benzoyl-pseudotropein. This alkaloid is important not merely because of its use in medicine but also because the base pseudotropine is isomeric with the base tropine found in atropine.

In the fourth group are hygrine $C_8H_{15}ON$, cuscohygrine, $C_{13}H_{24}ON_2$ and betahygrine, $C_{14}H_{24}ON_2$. These are comparatively simple compounds and are liquid at ordinary temperatures.

With the exception of ecgonine and anhydroecgonine, all of the bodies in the foregoing list are easily decomposable, splitting up when heated to from 80° to 100° C. with hydrochloric acid, or when boiled with alcoholic potassium hydroxide.

Cocaine has the following structural formula:



The characteristic group conferring the anesthetic properties is the benzoyl group.

It may be identified by treatment with strong acids and heating, the decomposition into methyl alcohol and benzoic acid being followed by the production of methyl benzoate with its very characteristic odor. It is easily decomposed by heat in the presence of moisture on solutions of its salts may not be sterilized by heat.

Much of the cocaine used in this country is prepared from the crude alkaloid which is manufactured in the countries where the plant grows. The alkaloids are extracted from the leaves by kerosene or some other cheap immiscible solvent in the presence of an alkali, the alkaloids being separated from the solvent with dilute sulphuric acid from which cocaine is precipitated by sodium carbonate. This crude substance represents about 90 per cent. of cocaine. A good deal of cocaine is manufactured in Germany from the Java coca leaves which contain chiefly cinnamyl cocaine. This alkaloid is hydrolyzed by boiling with diluted hydrochloric acid and the ecgonine so obtained treated with benzoic anhydride and methyl iodide. The other coca bases may also be converted into cocaine by a similar process as suggested by Liebermann (*B. Chem. G.*, 1888, xxi, 3196).

Description and Physical Properties.—

"Colorless crystals, or a white, crystalline powder. It is odorless, and is stable in the air. One Gm. of Cocaine is soluble in about 600 cc. of water, 6.5 cc. of alcohol, 0.7 cc. of chloroform, 3.5 cc. of ether, 12 cc. of olive oil, and in 30 to 50 cc. of liquid petrolatum, at 25° C. One Gm. is soluble in 270 cc. of water at 80° C. It is very soluble in warm alcohol.

"Cocaine melts between 96° and 98° C. Its saturated aqueous solution is alkaline to litmus paper. Its solution in diluted acids is laevorotatory. Heat about 0.1 Gm. of powdered Cocaine with 1 cc. of sulphuric acid for five minutes at 100° C., then cautiously mix with 2 cc. of distilled water: the aromatic odor of methyl benzoate is noticeable and on cooling crystals of benzoic acid separate.

"The ash from 0.5 Gm. is negligible. Dissolve 0.1 Gm. of finely powdered Cocaine in 1 cc. of sulphuric acid: not more than a slightly yellow tint is produced (readily carbonizable substances). Dissolve 0.3 Gm. of finely powdered Cocaine in 1 cc. of normal hydrochloric acid, gently warming, if necessary, to aid solution, and dilute with distilled water to 15 cc.: 5 cc. portions of this solution do not respond to the tests for cinnamyl-cocaine and for isoatropyl-cocaine under Cocaine Hydrochloridum."

The *British Pharmacopoeia* gives the following description: "In colorless monoclinic prisms. No odor; taste bitter, followed by a sensation of tingling and numbness. Soluble in 10 parts of alcohol (90 per cent.), in 4 parts of ether, in 0.5 part of chloroform, and in 24 parts of olive oil; almost insoluble in water. Melting point 98° C. The dry salt obtained by dissolving cocaine in water acidified, with hydrochloric acid, and evaporating the solution, responds to the tests described under 'Cocainae Hydrochloridum.'" Br.

Uses.—For most purposes cocaine hydrochloride is preferred to the base, but the latter is used in ointments and oily solution because of its greater solubility in fatty substances. Other salts of cocaine have been used in medicine. Cocaine borate has been recommended for ophthalmological uses. Cocaine hydriodide which occurs in colorless crystals moderately soluble in water, has been recommended by R. Marcus as being especially suitable for use by cataphoresis for the production of anesthesia. For medicinal uses, see Cocaine Hydrochloride.

Dose, one-eighth to one-fourth grain (0.008-0.016 Gm.).

Off. Prep.—Oleatum Cocainae, *N.F.*; Unguentum Cocaine, *Br.*

COCAINE HYDROCHLORIDUM. *U.S.*, *Br.* COCAINE HYDROCHLORIDE Cocain.

Hydrochl.

[Cocainum Hydrochloricum P. I.]

"[C₁₇H₂₁O₄N.HCl]." *U.S.* "Cocaine Hydrochloride, C₁₇H₂₁O₄N, HCl, is the hydrochloride of the alkaloid cocaine." *Br.*

Cocainea Hydrochloras, *U.S.* 1890, Cocaine Chloride. Hydrochlorate of Cocaine. Cocaina, Chlorhydricum, Chlorhydrate de Cocaine, *Fr. Cod.*, Cocainum hydrochloricum, *P. G.*, Cocainhydrochlorid, *G.*, Cloridrato di Cocaina, *It.*, Cloruro de Cocaina, *Sp.*

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Description and Physical Properties.— "Colorless, transparent crystals, lustrous leaflets, or a white, crystalline powder. It is odorless and is stable in the air. One Gm. of Cocaine Hydrochloride is soluble in 0.4 cc. of water, 3.2 cc. of alcohol, and in 12.5 cc. of chloroform, at 25° C. One Gm. is soluble in 2 cc of alcohol at 60° C. It is soluble in glycerin and insoluble in ether.

"Melting point not below 183° C. Add five drops of a solution of chromium trioxide (1 in 20) to 5 cc. of a solution of Cocaine Hydrochloride (1 in 50): a yellow precipitate is produced which redissolves on shaking the mixture. On the addition of 1 cc. of hydrochloric acid, a permanent, orange-colored, crystalline precipitate is formed. A solution of about 0.01 Gm. of Cocaine Hydrochloride in 1 cc. of distilled water yields on the addition of 2 cc. of tenth-normal potassium permanganate a violet, crystalline precipitate which appears brownish-violet when collected on a filter, and shows characteristic, crystalline aggregates under the low power of a microscope. Heat about 0.1 Gm. of powdered Cocaine Hydrochloride with 1 cc. of sulphuric acid for five minutes, then cautiously mix with 2 cc. of distilled water: the aromatic odor of methyl benzoate is noticeable and on cooling crystals of benzoic acid separate. Silver

nitrate T.S. produces in an aqueous solution of the salt (1 in 20) a white precipitate insoluble in nitric acid.

"The ash from 0.5 Gm. is negligible. Dissolve 0.5 Gm. of Cocaine Hydrochloride in 1 cc. of sulphuric acid: not more than a slightly yellow tint is produced readily carbonizable substances). A solution of 0.5 Gm. of Cocaine Hydrochloride in 10 cc. of distilled water requires for neutralization not more than 0.5 cc. of fiftieth-normal sodium hydroxide, using one drop of methyl red T.S. as indicator. Mix 5 cc. of an aqueous solution of the salt (1 in 50) with 0.3 cc. of normal sulphuric acid and 0.1 cc. of tenth-normal potassium permanganate: the violet color does not disappear entirely within a half hour (cinnamyl-cocaine). Dilute 5 cc. of an aqueous solution of the salt (1 in 50) in a beaker with 80 cc. of distilled water, add 0.2 cc. of ammonia T.S. and stir the solution vigorously during five minutes, occasionally rubbing the sides of the beaker with a stirring rod: a crystalline precipitate of cocaine is formed and the supernatant liquid is clear (isoatropyl-cocaine). The presence of 0.5 per cent. of isoatropyl-cocaine will prevent the formation of nearly all of the precipitate, and will cause the supernatant liquid to be milky." *U.S.*

"In colorless prismatic crystals, or a crystalline powder. No odor; taste bitter, followed by a sensation of tingling and numbness. Soluble in 0.5 part of water, and in 3 parts of alcohol (90 per cent.); insoluble in olive oil. Melting point 182° to 186° C Yields the reactions characteristic of chlorides. An aqueous solution is neutral to litmus, and when applied to the eye dilates the pupil. When moistened with nitric acid, the mixture evaporated to dryness, and 1 millilitre of alcoholic solution of potassium hydroxide added, a characteristic odor is evolved, recalling peppermint. The addition of 3 drops of N/10 solution of potassium permanganate to a solution of 0.1 gramme of the salt in 5 millilitres of water to which 3 drops of diluted sulphuric acid have been added, gives a violet color, which, if dust is excluded, does not fade in half an hour (absence of cinnamyl-cocaine and certain other coca alkaloids). If 0.1 gramme is dissolved in 100 millilitres of water in a glass beaker, 0.25 millilitre of solution of ammonia stirred in and the mixture set aside for fifteen minutes, the sides of the beaker being occasionally and not too vigorously rubbed with a glass rod, a crystalline deposit separates leaving the supernatant liquid clear (limit of amorphous alkaloid). 0.05 gramme dissolves in 1 millilitre of cold sulphuric acid or cold nitric acid without coloration but with hot sulphuric acid the salt chars, evolving an agreeable odor and yielding a sublimate of benzoic acid. Loses not more than 1 per cent. of its weight when dried at 100° No appreciable ash." *Br.*

D. Scherbatschew recommends for differentiating cocaine and several of its commoner substitutes placing three drops of the aqueous solution of the suspected substance on a glass slide and adding one drop, respectively of each of the following reagents: (1) Ten per cent. solution of NH_3 . (2) Ten per cent. solution of KOH . (3) A saturated solution of NaHCO_3 . Stovaine and holocaine give precipitates with all three reagents; betaeucaine gives only a slight precipitate with KOH and none with the other two; nirvanine gives a precipitate with NH_3 and a slight one with KOH but none with NaHCO_3 ; alypine precipitates decidedly with NH_3 and KOH , but not with NaHCO_3 ; novocaine precipitates with KOH but not with the other two. Cocaine and tropacocaine are identified by Hankin's KMnO_4 test.

Alphaeucaine hydrochloride gives a yellow precipitate when 5 cc. of a 1 per cent. solution are treated with three drops of a 5 per cent. solution of chromic acid. Cocaine hydrochloride does not. Betaeucaine hydrochloride when rubbed with dry mercurous chloride and then moistened with alcohol yields no color, cocaine hydrochloride when similarly treated turns grayish black. Holocaine hydrochloride gives in aqueous solution a violet precipitate with calcium hypochlorite, cocaine hydrochloride does not. Cocaine and procaine are distinguished by the potassium permanganate test (see Procaine Hydrochloridum).

Batta and Jenot describe in detail (*Chem. News.*, 1921, cxxiii, 65) a number of tests for distinguishing between cocaine, stovaine and procaine.

Uses.—It is necessary to distinguish clearly between the local and systemic effects of cocaine. When locally applied cocaine is a paralyzant to the peripheral ends of the sensory nerves, and to a lesser degree to the motor nerves, and stimulating to the muscular coats of the blood vessels. As a result of these actions when painted over mucous membranes it causes blanching of the part and diminished sensation. It produces not only lessened sensibility to pain and touch but also of the acuity of the special senses, thus it diminishes in the mouth the power of taste and in the nose that of smell.

Systemically it is a stimulant to all parts of the central nervous system including the brain, the spinal cord, and the medulla. Its effects upon the brain are shown by an exaltation of the intellectual faculties similar to that which is produced by caffeine. In overdose it produces a delirium somewhat suggesting that of atropine, to which it is chemically related. Its action upon the spinal cord is shown by increased activity of the reflexes but the convulsions which are seen in cocaine poisoning both in the lower animals and in man seem to be due to an action upon

the motor area of the brain, rather than to its effect on the cord. The effects on the medullary centers are shown by an increase of the rapidity of the respiration and sometimes also of its depth. After toxic doses the primary stimulation is followed by a depression of the respiratory center. The blood pressure is elevated chiefly through an action upon the vasomotor center, although there is some evidence that it also stimulates the heart. Concerning the changes in the pulse rate there is difference of opinion. According to Reichert (*P. M. J.*, 1902) small doses slow the pulse rate by stimulating the cardio-inhibitory center, moderate quantities increase the rate by depressing the inhibitory mechanism, while after large toxic doses there may be a second slowing of the heart through depression of its motor ganglia. Cocaine in moderate quantities also stimulates both the voluntary and involuntary muscle fibers. It appears also to have some effect upon the nutritive processes since it causes a marked rise in the bodily temperature. Whether this increase in temperature is due to a direct action upon the thermogenic centers or is simply the result of muscular activity, is as yet not definitely settled. When instilled into the eye it causes dilatation of the pupil, usually without paralysis of accommodation. The widening of the pupil seems to be the result of an action upon the peripheral ends of the sympathetic nerve and can be further increased by the instillation of atropine.

Cocaine is used in medicine both as a local and a systemic remedy. Internally it is of value as a circulatory and respiratory stimulant and is occasionally of use as a cerebral stimulant or as a tonic. Its employment, however, in any condition which requires prolonged administration of the drug is fraught with so great danger of formation of a habit that it is rarely justifiable. In narcotic poisonings the simultaneous stimulation of the respiration, circulation, and cerebrum makes it a remedy of particular value.

The most important use of cocaine is as a local application to mucous membranes either for the purpose of contracting the blood vessels or of lessening sensation. For the former action it is useful to relieve congestions such as hay fever, coryza, or laryngitis, and to control or prevent hemorrhage from the nose and throat. There are two great drawbacks to cocaine in this use, the first that the primary contraction of the blood vessels is liable to be followed by a reactive relaxation, and the second is the ever present peril of habit-formation. As a local anesthetic it is useful in operations on the eye, nose, throat, etc., in painful hemorrhoids, fissure in ano, vomiting, gastralgia, and other painful diseases of the mucous membranes. While cocaine passes

through all mucous membranes with greater or less ease, the unbroken skin offers a practically impassable barrier. Nevertheless, the drug is often used as a local anesthetic, especially for operative purposes, in all parts of the body. To obtain its action it is necessary that the drug be introduced beneath the skin in some manner; it may be either simply injected hypodermically or introduced into the vicinity of the large nerve trunks, or even injected into the spinal canal. The methods of using cocaine as a local anesthetic are too numerous and complex for consideration in this work and the reader is referred to treatises on Surgery. There is a widespread belief among both pharmacists and physicians that solutions of cocaine cannot be sterilized by heat without danger of decomposition, but a number of chemists have shown that if the solution is not allowed to become alkaline the degree of hydrolysis is insignificant.

Cocaine is also useful for the purpose of dilating the pupil, where paralysis of accommodation is not desired, as for example in ophthalmoscopy.

For local application to mucous membranes an aqueous solution of one of the salts of cocaine, ordinarily the hydrochloride, is usually preferred; Gross, however (*A.E.P.P.*, 1910, lxiii, p. 80) presents evidence that the basic cocaine is a much more powerful anesthetic than its salt and some authorities give preference to oily solutions of basic cocaine.

TOXICOLOGY.—As has been pointed out by Kamenzove (*A.I.P.T.*, 1911, xxi, p. 5) there are two distinct types of cocaine poisoning, one characterized by circulatory failure and the other by neurotoxic symptoms. The first type is usually seen after relatively small doses of the drug in persons who possess an idiosyncrasy against it. The prominent symptoms are pallor of the face, vertigo, nausea, failure of the pulse, and usually more or less complete loss of consciousness. The treatment of this type of poisoning is to place the patient in a horizontal position, give rapidly acting stimulants such as hypodermic injections of ammonia or camphor. Kamenzove believes that these symptoms are due to arterial spasm causing anemia of the brain.

The other group of cocaine poisonings is characterized by delirium, increased reflexes, more or less violent convulsions, the pulse usually being rapid and fairly strong but later may become weak, and syncope and cyanosis may intervene. The delirium is frequently associated with hallucinations and at times the patient may develop a violent mania of even homicidal character, as in a case reported by Mattison. In fatal cases death is usually due to respiratory failure although the circulation is also depressed.

In the treatment of cocaine poisoning, as the alkaloid rarely en-

ters the system through the alimentary canal, emptying the stomach and the use of chemical antidotes is generally not indicated. Eggleston and Hatcher (*J.P.Ex.T.*, 1919, xiii, p. 433) from an experimental study highly recommend, in the treatment of cocaine poisoning, the intravenous injection of epinephrin combined with artificial respiration. Nielsen and Higgins (*J. Lab. Clin. M.*, 1923, viii, 440) finds that pituitary solution exercises both a preventive and curative effect. In the convulsive type of poisoning, Tatum (*J.A.M.A.*, 1925, lxxxiv, 1177) finds that the intravenous injection of barbitol sodium is of much value provided it is administered promptly. The assertion that calcium chloride is antidotal to cocaine has been shown erroneous by Weiss (*J.A.M.A.*, 1923, lxxxi, 1282).

The habitual use of cocaine as a narcotic stimulant has reached an extent of sociological importance. In the United States the conditions under which it may be prescribed or dispensed are strictly limited both by Federal and in many states, by state laws. (See *U.S. Pub Health Rep.*, 1916, xxxi, and 1924, xxxix.) The cocaine habit is not only one of the most seductive but also one of the most rapidly injurious and difficult of eradication of all drug habits. The characteristic symptoms are changes in the mental and moral qualities, especially characterized by alternate periods of exaltation and depression, loss of appetite and of weight, peculiar pallor of the skin, insomnia, and general failure of health. A symptom which is seen in many cases and is said to be characteristic of chronic cocaine poisoning, is a sensory hallucination, as of some foreign body under the skin or of insects crawling over the person.

Dose, of the salts of cocaine, from one-fourth to one-half grain (0.016-0.03 Gm.). Source: Wood 1926

St. Louis Exhibition 1904—Grand Prix and Gold Medal.

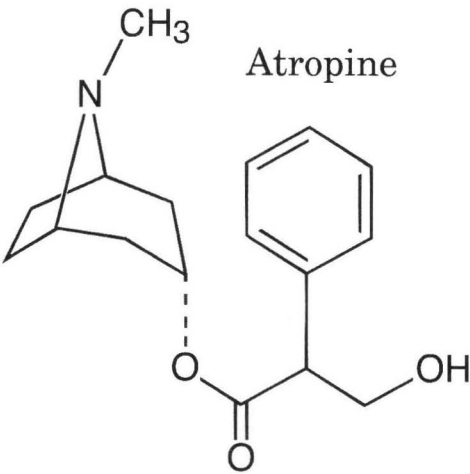
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Chapter 3: Atropine and the Tropeines

by Percy May, D.Sc. (Lond.), F.I.C.

Atropine was discovered in 1831 in the roots of the belladonna plant, and is a strongly poisonous alkaloid. Its chief use in medicine depends upon its action in dilating the pupil and paralysing the accommodation of the eye, and it is also used to check the inhibition of the heart arising from administration of chloroform and the depressant action of morphine on the respiratory centre.

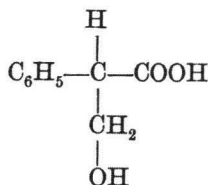
Atropine is an ester, and on hydrolysis yields a basic substance, tropine, and optically inactive tropic acid (1). It has been shown that the alkaloid hyoscyamine, which is also obtained from belladonna and is laevo-rotatory, is the ester of tropine with laevo-tropic acid (2), and therefore atropine appears to be racemic hyoscyamine. This view of the nature of atropine has been confirmed by Ladenburg (3), and dextro-hyoscyamine has also been prepared by the union of tropine with dextro tropic acid (4).

The pharmacology of these three stereo-isomerides, *d*-hyoscyamine, *l*-hyoscyamine, and the racemic form, atropine, has been investigated by Cushny, (5) using the frog as the subject of the experiments. It was found that all three were alike in certain respects, but that with regard to some aspects of their action dextro-hyoscyamine was the strongest and the levo variety the weakest, while with other effects of the drug exactly the reverse was the case. In all cases the action of atropine was intermediate between that of the two optically active forms, and this fact is explained by Cushny by the assumption that atropine is probably decomposed in solution into its two active components.

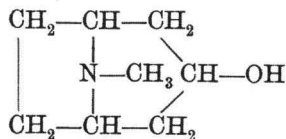
As atropine is the ester of tropine with racemic tropic acid, it is obvious that a knowledge of the constitution of these two substances is necessary in order to know that of atropine.

Tropic acid is a relatively simple substance, being indeed a homologue of mandelic acid, and having the constitution—

This view of its structure has been confirmed by a synthesis of the acid (6). The question of the constitution of tropine is one which has presented far greater difficulties, but thanks to the researches of Ladenburg, Merling, Willstätter, and others, our knowledge of the constitution of this substance is as complete as that of any alkaloid, and there is no doubt that it is represented by the formula and this has been confirmed by Willstätter's brilliant synthesis (7).



The constitution of this substance is of great importance, as not only does it show that atropine and hyoscyamine are represented by the formula—

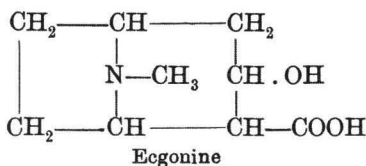
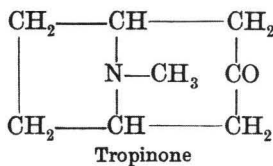
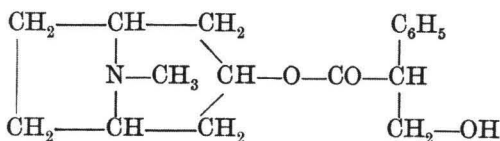


but it also explains the constitution of many other alkaloids which are derivatives of it.

For example, when tropine is heated with sodium and amyl alcohol, it is converted

into a substance which is stereoisomeric with it (8), and which is identical with the substance pseudo-tropine, obtained by the hydrolysis of the coca alkaloid, tropa-cocaine (benzoyl-pseudo-tropine). Both tropine and

pseudotropine yield the same substance on oxidation, namely, tropinone, and this on reduction yields pseudo-tropine and not tropine itself—



It has been shown that cocaine is a derivative of ecgonine, which is in turn a carboxylic acid of tropine, and hence our knowledge of the constitution of this important alkaloid is also dependent on that of tropine.

1) **Kraut**, *Annalen*, 128, 1863, 273; 133, 1865, 87; 148, 1868, 236;

Lossen, *Annalen*, 131, 1864, 43: 138, 230

2) **Gadamer**, *A. Pharm.*, 239, 1901, 294.

3) **Ladenburg**, *Ber.*, 21, 1888, 3065

4) **Amenomiya**, *A. Pharm.*, 240, 1902, 498

5) **Cushny**, *Journ. of Physiol.*, 30, 1903, 176.

6) **Ladenburg and Rügheimer**, *Ber.*, 13, 1880, 376; *Annalen*, 217, 1880, 74.

7) **Willstätter and Iglauer**, *Ber.*, 33 1900, 1170, **Willstätter** *Ber.* 34, 1901, 129, 3163; *ibid.*, *Annalen*, 317, 1901, 307.

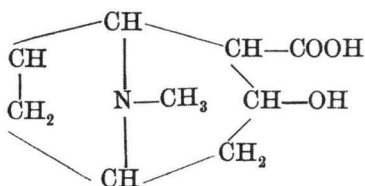
8) Tropine is optically inactive, and so also is pseudo-tropine; the isomerism is dependent on molecular asymmetry (*cis-trans* isomerism).—(**Barrowcliff** and **Tutin**, *J.C.S.*, 95, 1909, 1966.)

Cocaine and the Local Anesthetics

by Percy May, D.Sc. (Lond.), F.I.C.

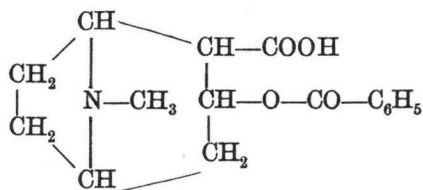
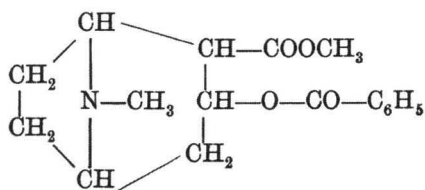
The alkaloid cocaine was discovered in coca leaves in 1860 (1). It had long been known that the South American Indians were in the habit of chewing these leaves as a stimulant to enable them to stand great exertion without fatigue. The first use of cocaine in this country was for a similar purpose, but its great importance among alkaloids at the present time is due chiefly to Koller's important discovery that cocaine is a powerful and rapid local anesthetic.

By hydrolysis with alkalis, cocaine yields ecgonine, benzoic acid, and methyl alcohol. Ecgonine was shown by Willstätter to be a carboxylic acid of tropine—

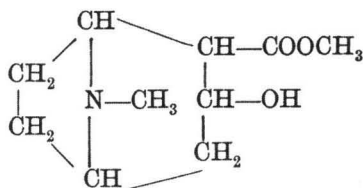


and by treatment with benzoyl chloride to yield benzoyl-ecgonine, in which the hydroxyl group is converted into O-CO.C₆H₅; this on conversion into its methyl ester yields cocaine, which therefore has the formula—

It is found that the free carboxylic acid, benzoyl-ecgonine itself, has no local anesthetic action, but that any of its alkyl esters, such as ethyl, propyl, etc., resemble its methyl ester, cocaine, in having this action (2). This applies only to the aliphatic esters, as the aromatic do not appear to have been prepared as yet. The effect of esterification is probably accounted for by an alteration of the anchoring group—



Benzoyl-ecgonine
(type of first series of esters)



Ecgonine methyl ester
(type of second series of esters)

Ecgonine can be esterified in the usual way, leaving the hydroxyl group intact, and in this manner another series of esters can be obtained. Ecgonine methyl ester has no local anesthetic action, but can be converted into cocaine by benzoylating the hydroxyl group. In this case, however, the nature of the group used to esterify the hydroxyl is important, for if the benzoyl group is replaced by others, the anesthetic property is lost or greatly diminished.

Thus truxilline (3) (isatropyl-cocaine) has no anesthetic action, but is a strong cardiac poison, and Ehrlich (4) found that, of several different cocaine derivatives, such as isatropyl-cocaine, valeryl-cocaine hydriodide, and phenylacetyl-cocaine hydriodide, the last named was the only one which had anesthetic properties, but to a less degree than cocaine. All of these have a characteristic toxic effect on the liver, and differ from cocaine only in having the benzoyl group replaced by the one named.

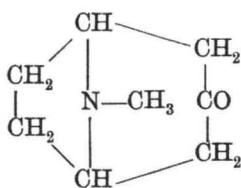
Coca leaves, which are the only commercial source of cocaine, contain various other alkaloids, most of which are, however, devoid of the useful physiological properties of cocaine. These other alkaloids are amorphous substances which yield ecgonine on hydrolysis, and therefore, owing to the high price of cocaine various methods have been devised to utilize them in improving the yield of cocaine obtainable from the leaves. According to one method (5), the alcoholic solution of the amorphous bases is boiled with hydrochloric acid, filtered from the precipitated organic acids, and practically pure ecgonine hydrochloride obtained by evaporation of the filtrate. By means of benzoyl chloride or benzoic anhydride this is converted into benzoyl-ecgonine, which is then esterified with methyl alcohol giving cocaine. Various modifications of this method have also been devised (6).

Cocaine has several disadvantages when used for hypodermic injection, one of the most serious being that its solutions do not keep well, but become mouldy and decompose on boiling, so that they cannot be readily sterilized. For this reason, and also on account of the high price of cocaine, various attempts have been made to prepare analogous compounds which it was hoped would resemble cocaine in its useful physiological effects. As cocaine is a derivative of ecgonine, which is closely related to tropine, and as atropine, one of the esters of tropine, has a slight anesthetic action, various attempts have been made to prepare substances from tropine which should have an action resembling that of cocaine. Several synthetic tropeines have been prepared... but none of these are of value as substitutes for cocaine. Strangely enough, however, a natural tropeine was discovered in Java coca leaves (7), which is

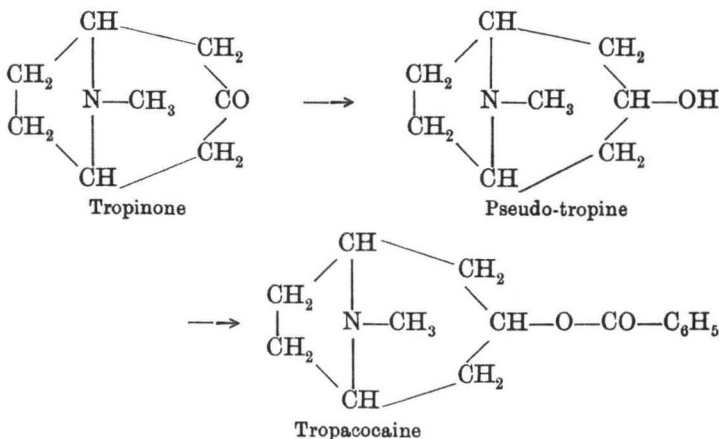
a stronger local anesthetic than cocaine (8). This substance, which is called tropacocaine, also has the advantage over cocaine in being less toxic and more resistant to micro-organisms, and hence its solutions can be preserved for some length of time. It is the benzoyl ester of pseudo-tropine (9), which only differs from ordinary tropine in its space configuration. It differs from cocaine and atropine in having no mydriatic action, and in this respect it resembles the other pseudo-tropeines, such as those of mandelic acid and tropic acid.

It will thus be seen that the tropeines derived from tropine itself have a strong mydriatic action, but only a weak anesthetic action, while their stereo-isomerides, derived from pseudo-tropine, have no mydriatic action, but are powerful local anesthetics.

Pseudo-tropine is obtained from tropine by heating it with sodium amylate (10) and it is also obtained from tropinone—
by electrolytic reduction in acid solution (11).



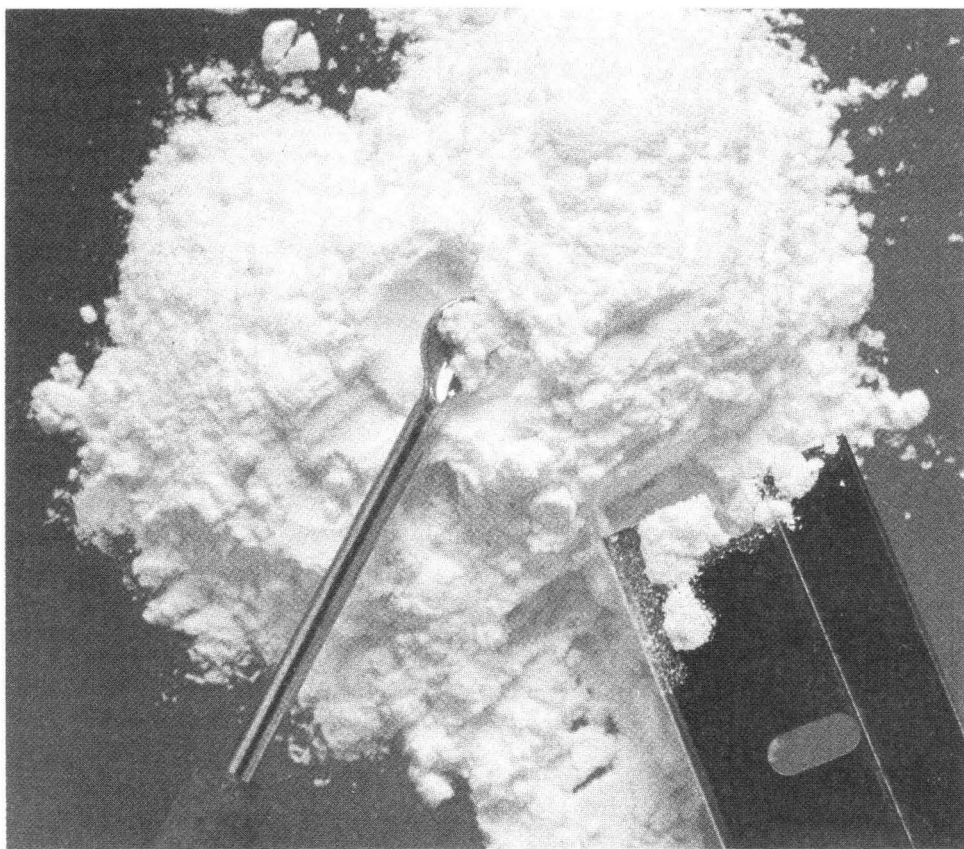
It should be pointed out that tropinone is obtained by oxidizing tropine with chromic acid (12), or with permanganate in acid strong acid solution (13), or with other oxidizing agents (14). Pseudo-tropine is then easily converted into tropacocaine by means of benzoyl chloride—



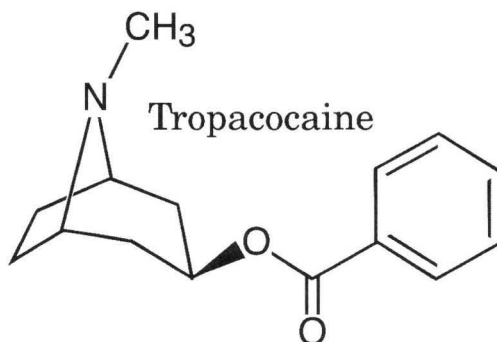
- 1) **Neumann**, *Annalen*, 140, 1860, 213.
- 2) **Merck**, *Ber.*, 18, 1885, 2954; 21, 1888, 48;
Novy, *Amer. Chem. Journ.*, 10, 1888, 147.
- 3) **Liebermann**, *Ber.*, 21, 1888, 2347.
- 4) **Ehrlich**, *Deutsche med. W.*, 32, 1891, 717.

- 5) **Liebermann** and **Giesel**, *D.R.P.*, 47,602.
- 6) **Einhorn** and **Klein**, *Ber.*, 21, 3335; *D.R.P.*, 47,713.
Farbw. Hoechst, *D.R.P.*, 76,433.
- 7) **Giesel**, *Pharm. Ztg.*, 1891, 149.
- 8) **Chadbourne**, *B.M.J.*, 1892, 402.
- 9) **Liebermann**, *Ber.*, 24, 1891, 2336, 2587; 25, 1892, 927.
- 10) *D.R.P.*, 88,270.
- 11) *D.R.P.*, 115,517.
- 12) **Willstätter**, *Ber.*, 29, 1896, 396.
- 13) *D.R.P.*, 117,628.
- 14) *Ibid.*, 117,629, 117,630, 118,607.

Source: May 1921



Chapter 4: Tropacocaine



by Horatio C. Wood, Jr. M.D.

Charles H. LaWall, Ph.M., D.Sc., Phar.D.

Heber W. Youngken, Ph.M., Ph.D.

John F. Anderson, M.D

Ivor Griffith, Ph.M

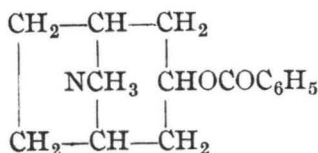
Tropacocaine. Benzoyl-pseudotropeine. $C_8H_{14}ON.C_7H_5O$.—This compound, belonging chemically to the class of Tropeines (see Atropine), was isolated by Geisel from a narrow-leaved coca plant from Java. (*Ber. d. Chem. Ges.*, xxiv, p. 2336.) It is obtained as an oil, which when quite dry solidifies in radiating crystals, melting at 49° C. It has a strong alkaline reaction, and is easily soluble in alcohol, ether, chloroform, benzene, and petroleum benzin. The hydrochloride, being freely soluble in water, is usually preferred to the base. It is decomposed by heating with hydrochloric acid into benzoic acid and pseudotropine, $C_8H_{15}ON$.

Tropacocaine resembles cocaine in its stimulant action upon the nerve centers, and also in its local anesthetic action. It differs from cocaine, however, in that it does not cause local constriction of the blood vessels, and that it has very little influence upon the pupil. Sollmann (*J.A.M.A.*, 1918, lxx, 216) has shown that it is approximately equal to cocaine in its anesthetic power and Eggleston and Hatcher that it is distinctly less toxic. It has been used chiefly in the so-called spinal anesthesia and a large number of surgeons have reported favorably upon it. A dose of one grain (0.06 Gm.) is ordinarily recommended, although a number of authors have used larger quantities without evil effects.

Tropacocaine has been used also as a local anesthetic in ophthalmic and pharyngological practice. It possesses an advantage over cocaine in being more stable in solution and easily sterilizable.

Source: Wood 1926

Tropacocaine
(Benzoyl pseudotropine)
 $C_{15}H_{19}O_2N$. M.W. 245



by M. Barrowcliff, M.B.E., F.I.C. and
Francis H. Carr, C.B.E., F.I.C.

Tropacocaine was discovered in Java coca leaves (Giesel, *Ber.* 1891, 24, 2336) and has since been found to be present in Peruvian coca (Hesse, *J. prakt. Chem.* 1902, 66, 401). Its isolation from crude cocaine is a matter of difficulty; hence it is technically prepared from tropine. Tropine is boiled with sodium amyloxide in amyl alcohol, prepared by dissolving sodium in dry amyl alcohol. By this treatment it is converted, to a large extent, into its stereoisomeride, ψ -tropine (Willstätter, *Ber.* 29, 936).

The base thus obtained is distilled in vacuo and crystallised from a mixture of benzene and light petroleum. About 65% of pseudotropine (m.p. 108°) is obtained, and 35% of a mixture of tropine and pseudotropine, which is mixed with the next batch of tropine to be converted. It is benzoylated in the same way as has been described under cocaine (Barrowcliff and Tutin, *J.C.S.* 1909, 95, 1970), and the resulting tropacocaine hydrochloride purified by recrystallisation from petroleum. M.p. 271° (Willstätter); 283° (Barrowcliff and Tutin).

Tropacocaine hydrochloride forms colourless crystals readily soluble in water. It should withstand permanganate to the same extent as does cocaine hydrochloride, when the same test is applied.

Tropacocaine is employed as a local anesthetic and closely resembles cocaine in its action. It is said to possess only one-half the toxicity of cocaine and to produce less dilation of the pupil of the eye. Anesthesia sets in more rapidly and is more prolonged than in the case of cocaine. In lumbar anesthesia tropacocaine is indicated as the most reliable and least dangerous of the drugs in use.

Source: Barrowcliff 1920

Benzoyl Ester of Ecgonine Using Benzoic Anhydride

An aqueous solution of Ecgonine (approx. one mol. of Ecgonine in one mol. of water), is heated to boiling temperature with somewhat more than the equivalent quantity benzoic acid anhydride (1 Mol.) is refluxed for about 1/2 to 1 hour.

Source: Liebermann 1889

Tropacocaine from Pseudo-tropine and Benzoic Anhydride

Approximately one mole of pseudotropine is heated with approx. one mol. of water and then refluxed with a slight excess of benzoic anhydride. The mixture is gently refluxed for approx 4 hours. The product is mixed with ether and hydrochloric acid. The aqueous layer is separated and diluted with more water. The aqueous mixture is extracted with half its volume with ether or appropriated solvent. The majority of unchanged pseudo-tropine remains in the aqueous layer. The ether solution is cooled, and the tropacocaine salt precipitated by the addition of an acid. Evaporation of ether will produce more tropacocaine. Refs.: Blount 1933

Tropine and pseudo-tropine both possess the same structural formula, for, on oxidation, they each yield tropinone, whilst the latter, when reduced, gives a mixture of the two hydroxy-bases (Willstätter and Iglaue, *Ber.*, 1900, 33, 1170). Willstätter concluded, therefore, that a *cis-trans*-isomerism, dependent on the relative positions in space of the hydroxyl and methyl groups, existed between tropine and pseudo-tropine. Objection to this explanation might be made on the ground that no quite parallel case of isomerism seems to have been observed, and it therefore appeared to the present authors that it should not be accepted unreservedly so long as another explanation is possible.

The tropine molecule contains two similar asymmetric carbon atoms, and the base should therefore be capable of existing in a racemic and an internally compensated form. The possibility of these two optically inactive modifications being represented by tropine and pseudo-tropine had been considered by Willstätter, but he rejected this explanation, as both bases, on oxidation, yielded the same ketone. It seemed to the present authors, however, that the possibility of the difference

between tropine and pseudo-tropine being dependent on the configuration of the two asymmetric carbon atoms was not entirely excluded, for each of these bases might undergo racemisation during the process of oxidation, thus yielding identical ketonic products. Tropinone would then be a mixture of the racemic and meso-ketonic bases, and this would account for its yielding both tropine and pseudo-tropine on reduction. On the other hand, if racemisation does not occur during the oxidation of tropine or pseudo-tropine, it was thought possible that two compounds so nearly related as racemic and meso-tropinones might be so similar in properties that their individuality had been overlooked.

In view of the above considerations, therefore, it would appear that the formation of pseudo-tropine by the action of sodium amyloxyde on tropine might be a process of racemisation, and this seemed to be in harmony with the experimental facts, since the change in question is never complete. Thus, in our experiments on the preparation of pseudo-tropine, about 35 per cent. of the basic product resulting from the treatment with sodium amyloxyde was found to consist of an uncrystallisable mixture of tropine and pseudo-tropine, and Willstätter mentions that the yield of pure pseudo-base obtained by him did not exceed 50 to 55 per cent. of that theoretically possible. It appeared, therefore, that the action of sodium amyloxyde on tropine resulted in the formation of an equilibrium mixture of this base and pseudo-tropine, just as the action of alkali on pilocarpine or isopilocarpine results in the production of an equilibrium mixture of these two stereoisomeric bases (Jowett, *Trans.*, 1905, 87, 794). This, however, is not the case, since the change is irreversible, no tropine being formed by the action of sodium amyloxyde on pseudo-tropine.

Apart from the question of the relation of tropine to pseudo-tropine, the individual configuration of each of these bases requires to be established. This point was considered by Gadamer (*Arch. Pharm.*, 1901, 239, 294), who drew the conclusion that tropine was internally compensated, since hyoscyamine yielded inactive tropine, even when hydrolysed only with water, and he did not consider it likely that a naturally occurring compound would be partially racemic. Much value should not, however, be attached to the grounds on which Gadamer based his conclusions, for partially racemic compounds do occur in nature, as an example of which prulaurasin may be quoted (Hérissey, *Compt. rend.*, 1905, 141, 959). Moreover, as proved in the present investigation, hyoscyamine always suffers some racemisation when liberated from its salts, and this change might occur in the tropine part of the molecule. That is to say, that if free hyoscyamine were partially racemic, the base,

when in the form of its naturally occurring salts, might, nevertheless, be a derivative of optically active tropine.

With the object, therefore, of definitely establishing the configuration of tropine and of pseudo-tropine, we have conducted experiments on the resolution of these bases, and some of their derivatives, by fractionally crystallising their salts with certain optically active acids. It may at once be stated that the results of these experiments point to the conclusion that both the bases in question are internally compensated compounds. The relation between them must, therefore, be of the nature of a *cis-trans*-isomerism, as concluded by Willstätter. (*loc. cit.*). Attempts were made to racemise tropine by heating the latter at high temperatures with hydrochloric acid, but these were unsuccessful.

Source: Barrowcliff 1909

Pseudotropine by Electrolytic Reduction of Tropine

1 kg of Tropine is dissolved with water and 0.4 kg of concentrated sulfuric acid on 4000 ccm. One brings this solution into a lead vessel serving as anode, in which an appropriately arranged lead cathode is. Best one selects a lead cylinder, the inside provided with slots, and inside the internal Cylinder an agitator. The electrolytic reduction is carried out at approx. 0° with 2.5 A/qdm anode surface. Unglazed porous porcelain diaphragms are used. After passage of any quantity of electricity one interrupts the current, isolates the formed Pseudotropine and the recovered Tropine is used again. Source: Merck 1902

See *Amphetamine Syntheses Industrial* for detailed description of electrolytic reduction apparatus.

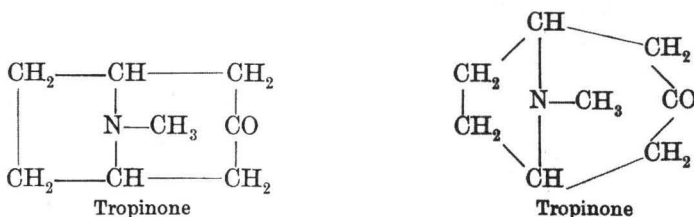
Tropineone by Oxidation of Tropine

For the explanation the representation serve the following example:

To a solution of 100 g tropine in 2 kg glacial acetic acid, which is warmed up continuously to 60 to 70° , one adds dropwise in the solution of 48 g chromic acid in 50 g water and 250 g glacial acetic acid under steady agitating by means of turbine. After registering the oxidant the solution short time is warmed up to 100° and separated with an excess of caustic soda in concentrated aqueous solution. From the alkaline liquid the tropinone is extracted with ether. Tropinone is obtained by evaporation of ether. The yield amounts to over 80 percent the computed quantity. Source: Willstätter 1896

Extraction of Pseudotropine

Example: After finished Reduction one extracts the contents of the hydrogen cell with caustic soda solution and extracts repeatedly with ether. Source: Chemische 1898



Pseudotropine by the Electrolytic Reduction of Tropinone

Example. 25 g Tropinone are solved with 11 g of concentrated sulfuric acid in water in 180 ccm and brought into the cathode area of a Electrolytic apparatus separated by a diaphragm, in whose anode region one is approximately in the concentration 1:10 diluted sulfuric acid. As electrodes appropriate lead sheets serve. One electrode with a current density of 1.2 Amp./qdm with 3.5 to 4 V, however also higher and low current densities and tensions are usable. A hydrogen development arises at the cathode only after passage of the Amp. hours theoretically necessary for the reduction of the tropinone. After termination of the reduction, pseudotropine is isolated in the way described above. Source: Merck 1900

Tropinone by the Oxydation of Tropine

In a solution of 100 g tropine in 2 kg water one pours in small portions a solution of 467 g potassium ferrocyanide and 60 g caustic soda in 2 kg water. The reaction is led in such a way, is not exceed maintained temperature. The formed tropinone can be driven-over with an excess of caustic potash and Isolated with ether. Merck 1901a

Tropinone by the Oxydation of Pseudotropine

Into a solution of 100 g pseudotropine and 2 kg water one adds in small portions a solution of 467 g potassium ferrocyanide and 60 g caustic soda in 2 kg water. The formed tropinone is isolated in the way indicated in the previous example. Merck 1901a

Tropinone by the Electrolytic Reduction of Tropine or Pseudotropine

180g Tropine or pseudotropine is dissolved in a mixture of 70 g of concentrated sulfuric acid and 650 g water. This solution is brought into the anode region of an electrolytic apparatus which can be cooled, whose cathode area is separated by a diaphragm contains diluted sulfuric acid. The current which can be introduced now is to possess a density of 3 A/qdm anode surface, but is still well applicable also higher and low current densities. After the passage of the necessary ampère hours the current is interrupted. The developed tropinone can be isolated then in well-known way. Source: Merck 1901

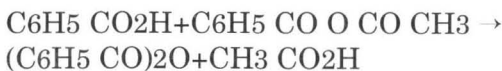
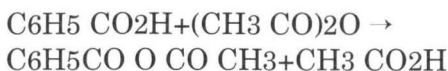
Method B: 180 g tropine or pseudotropine is dissolved with 70 g ammonium sulphate in 720 g water, on which sulfuric acid up to the neutralization is added. This solution is made alkaline with ammonia poured into the anode region of the electrolytic reduction apparatus, while in the cathode area a solution of 280 g ammonium sulfate in 800 g water. The further procedure is then exactly the same, as described 1 in the example. Source: Merck 1901

Tropine mixed with tropic acid can be obtained from atropine by hydrolysis with hydrochloric acid or a barium hydroxide solution.

Benzoic Anhydride

Prepared by H. T. Clarke and E. J. Rahrs

Checked by Roger Adams and P. K. Porter



Procedure

IN a 5-L. flask, provided with a two-hole stopper fitted with a 90-cm. fractionating column (1) and a dropping funnel, are placed 1500 g. of benzoic acid, 1500 g. of acetic anhydride, and 1 cc. of syrupy phosphoric acid. The mixture is very slowly distilled, at such a rate that the temperature of the vapor at the head of the column does not exceed

120° (Note 1). When 250 cc. of distillate has been collected, 250 g. of acetic anhydride is added, and distillation is continued. This process is again repeated, so that in all 2000 g. of acetic anhydride has been taken. Fractionation is then continued, fractions which distil respectively below 120°, at 120-130°, and at 130-140° being collected. Heating is continued until the temperature of the reaction mixture in the flask reaches 270°.

The residue is fractionally distilled under reduced pressure, resulting in the collection of fractions which boil respectively below 165°, at 165-210°, and at 210-220°, all under 19-20 mm pressure (Note 2). The lower fractions are mixed with the fraction which boils at 120-130°, and distilled as before after the addition of one drop of phosphoric acid, when a further quantity of material boiling at 210-222°/20 mm. is obtained. This fraction, amounting to 1100-1200 g., consists of crude benzoic anhydride. The lower-boiling fractions may be redistilled until they become too small to justify further work.

The fraction which boils at 120-130° under atmospheric pressure is redistilled, yielding further quantities of acetic acid (below 120°) and acetic anhydride (130-140°).

The crude benzoic anhydride (which is apt to supercool without crystallizing) contains a small proportion of an oily impurity which causes the product to turn yellow on standing; it is recrystallized by dissolving in benzene (50 cc. for each 100 g.) then adding just enough petroleum ether to cause a cloudiness (about 100 cc is required) and chilling, when the pure anhydride separates in perfectly colorless and odorless crystals melting at 43°. The first crop amounts to about 50 per cent of the crude material taken; the mother liquors are freed of solvent by distillation on the water bath, and the residue distilled under reduced pressure, when a further quantity of pure material can be obtained by recrystallizing the distillate boiling at 210/220°/19 mm. If this process is repeated until the mother liquor becomes too small in amount to redistil satisfactorily, the yield of pure benzoic anhydride melting at 43° amounts to 1000-1030 g (72-74 per cent of the theoretical amount). It is generally more convenient to distil the mother liquors only once or possibly twice, under which conditions a somewhat lower yield is obtained. The remaining mother liquors may then be mixed with a subsequent preparation.

Notes

1. As it is probable that the equilibria between the two acids and the three anhydrides are established in reactions of relatively low velocity, the distillation must be carried on very slowly, in spite of the catalytic action of the phosphoric acid. The intermediate fractions

contain the mixed anhydride, detectable by its odor, which resembles that of acetophenone.

2. Owing to the high boiling-point of the end-product, the second stage must be conducted under reduced pressure. The temperatures indicated depend, of course, upon the pressure under which the distillation is carried out, and allowances will have to be made for pressures differing materially from 20 mm.

3. Although the yield above quoted is by no means quantitative, the only reason why it should not be made nearly so by continual redistillation of the various fractions in presence of the catalyst lies in the length of time required for the process. This, however, could be avoided if a large number of runs were to be made, when the intermediate fractions could be worked over repeatedly with each subsequent batch, until practically nothing but acetic acid and benzoic anhydride remained.

Other Methods of Preparation

Benzoic anhydride has been prepared in rather a poor yield by the action of benzoyl chloride on sodium benzoate (2), barium oxide at 150° (3) benzoic acid at 160-200° (4), sodium nitrite (5), lead nitrate (6), or anhydrous oxalic acid (7); also by treating sodium benzoate with phosphorus pentachloride (8) or sulfur chloride (9).

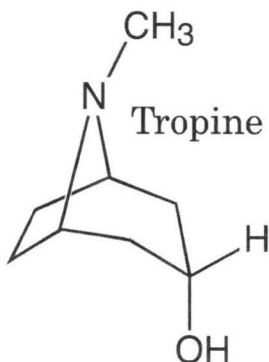
More important methods consist in treating benzotrichloride with sulfuric acid (10), and in the action of sodium carbonate upon benzoyl chloride in presence of pyridine (11).

By heating benzoic acid with acetic anhydride in a closed vessel at 220°, a poor yield of benzoic anhydride is obtained (12), a 50 per cent yield is obtained by boiling benzoic acid with three times its weight of acetic anhydride and distilling the mixture (13).

Numerous patents have appeared in which benzoic anhydride has been prepared: by the action of benzenesulfochloride upon sodium benzoate (14), by the action of chlorosulfonic acid upon potassium benzoate (15); by the action of silicon tetrachloride upon sodium benzoate (16); by the action of sulfuryl chloride upon a mixture of calcium benzoate and sodium sulfate or sodium chloride (17); by the action of sulfuryl chloride upon a mixture of 2 mols. of sodium benzoate and 1 mol. of calcium benzoate (18); by the action of sulfur dioxide and chlorine upon sodium benzoate (19); by the action of sulfuric anhydride upon a mixture of benzoic acid and sodium benzoate (20); by the action of a mixture of sulfuric anhydride and carbon tetrachloride on sodium benzoate.

It is probable that some of these patented processes would be more suitable for the commercial preparation of benzoic anhydride, but the method given in the procedure is satisfactory for the laboratory.

- 1) *Ind. Eng. Chem* 15, 349 (1923)
- 2) *Ann.* 87, 73 (1853).
- 3) *Ann.* 128, 127 (1863).
- 4) *Ann.* 226, 5 (1884).
- 5) *Gazz. Chim. Ital.* 20, 655 (1890).
- 6) *Ber.* 17, 1282 (1884).
- 7) *Ann.* 226, 15 (1884).
- 8) *Jahresb.* 1854, 409.
- 9) *Jahresb.* 1856, 464.
- 10) *D. R. P.* 6,685; *Frdl.* 1, 24 (1877-87).
- 11) *Gazz. Chim. Ital.* 22, 215 (1892); *J. prakt. Chem.* (2) 50, 479 (1894).
- 12) *Ann* 226, 12 (1884)
- 13) *Ber.* 34, 184 (1901).
- 14) *D. R. P.* 123,052; *Frdl.* 6, 35 (1900-02)
- 15) *D. R. P.* 146,690; *Frdl.* 7, 28 (1902-04).
- 16) *D. R. P.* 171,146; *Frdl.* 8, 69 (1905-07).
- 17) *D. R. P.* 171,787; *Frdl.* 8, 68 (1905-07).
- 18) *D R P.* 161,882; *Frdl.* 8, 66 (1905-07).
- 19) *D. R. P.* 210,805; *Frdl.* 9, 68 (1907-10).
- 20) *D. R. P.* 286,872; *Frdl.* 12, 77 (1914-16).
- 21) *D. R. P.* 290,702; *Frdl.* 12, 79 (1914-16).

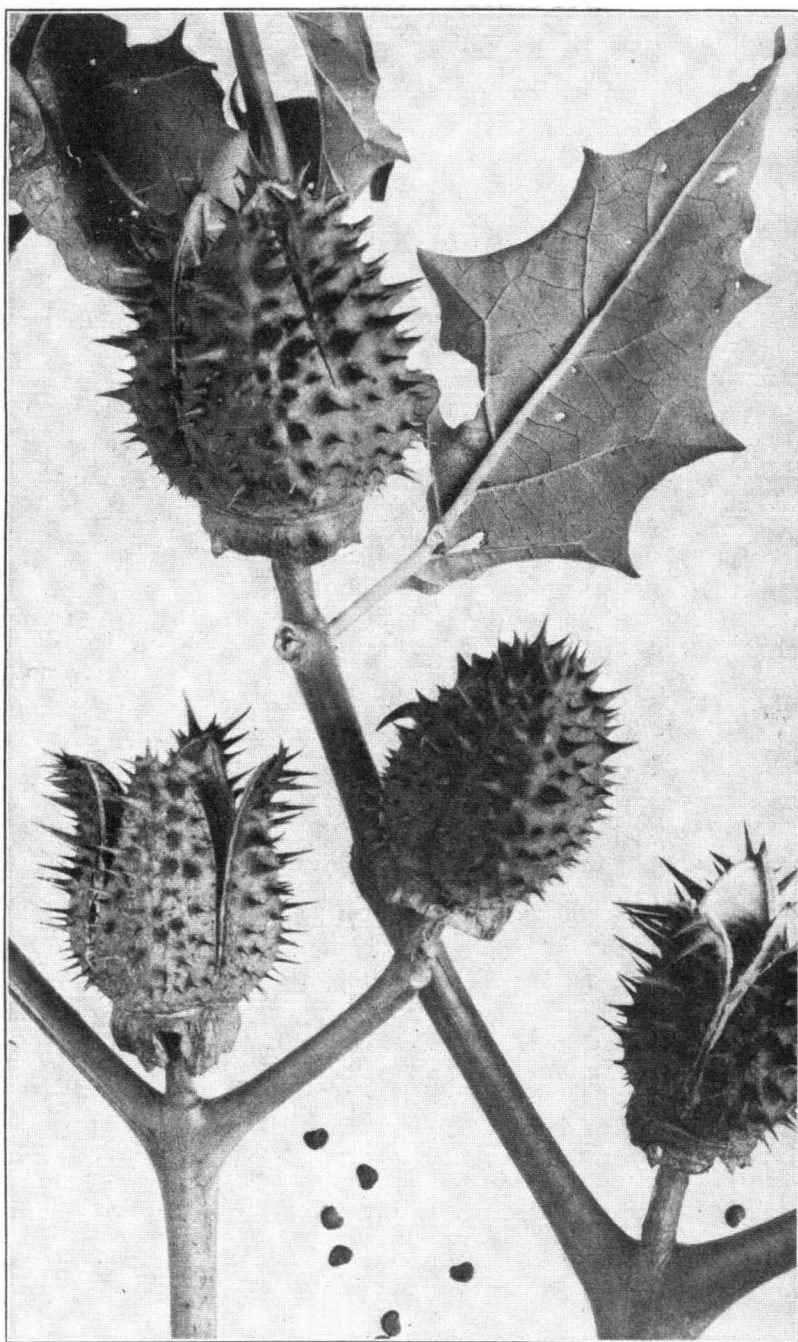


Chapter 5: Narcotic Daturas

by W.E. Stafford

In early accounts of the aborigines of America, both north and south of the Equator, we find repeated references to the use of various daturas as narcotics. The Quichuas of Peru put the seeds of *datura* into their azua, or fermented corn beer, to make it more intoxicating. They believed that the visions thus produced were supernatural and, like the remote Zuñis of New Mexico, they resorted to *datura* seeds in order to divine the hiding place of some precious object or to detect the thief who had stolen it. The professional Indian hechiceros of Spanish America were prosecuted by the church authorities for using narcotics in their practices of idolatry and witchcraft, very much as were the *datura* doctors of India for dispensing *datura* to criminals; and in the New World as in the Old World, *datura* seeds were administered in various ways as a love potion or aphrodisiac. Another remarkable parallel may be seen in the religious use of the drug. Among the Aztecs the seeds of a certain *datura* were held sacred and the spirit of the plant was invoked to expel evil spirits, recalling the exhortations of the priests, or physicians, of ancient Babylon and the necromancers of medieval Europe. In the Andes of South America Indian priests used *datura* seeds to produce delirium, recalling the use of intoxicants to induce frenzy by the Pythiae in consulting the famous oracle of Apollo at Delphi.

M. de la Condamine, while exploring the Rio Marañon in 1743, found the Omagua Indians inhabiting the banks of that river addicted to narcotics, one of which was referred by him to *Datura arborea*, the plant "called by the Spaniards *floripondio*, with flowers shaped like a drooping bell, which have been described by Père Feuillée (1)." Miss Alice Eastwood, while exploring southeastern Utah, came upon an abundance of *D. meteloides*, and she calls attention to the occurrence of its seed-pods "in the ruins of the ancient people who once filled this land and guarded every spring with towers of stone (2)." Stephen Powers found this same plant in use as an intoxicant and hypnotic by the priests and wizards of the Yokuts Indians inhabiting the banks of the Tule River and Lake Tulare in California (3). Dr. Edward Palmer states that a decoction of the plant is given by certain California Indians to their young women to stimulate them in dancing, and that an extract of its root is used as an intoxicant by the Pah-Utes (4). Other authorities state that the Mariposan Indians of California, including the Noches, or Yokuts, already mentioned, use a decoction of *Datura meteloides* in the ceremonial initiation of their youths into the status of manhood; and the



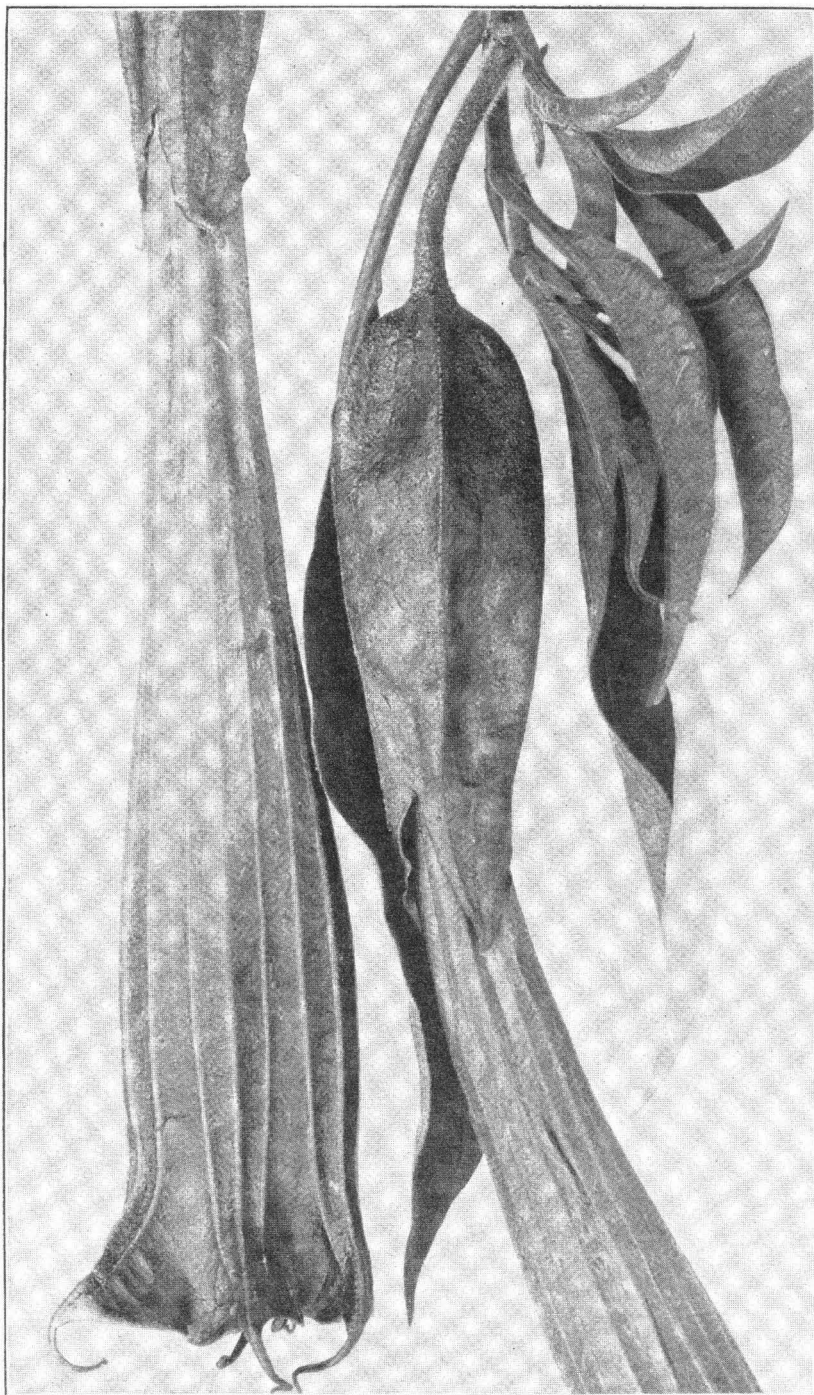
THE JAMESTOWN WEED, *Datura stramonium* L., WHICH INTOXICATED THE BRITISH SOLDIERS SENT TO QUELL BACON'S REBELLION. NATURAL SIZE.

medicine men of the Hualpais, or Walapais, belonging to the Yuman stock, indulge in a sacred intoxication by breaking up the leaves, twigs, and root of this plant to make a beverage which induces an exhilaration accompanied by prophetic utterances (5).

Origin of the Name Jimson, or Jamestown Weed

The narcotic properties of *Datura stramonium* are well known to our own southern Indians as well as to the Mexicans (6). Hernandez called attention to the fact that its fruit causes insanity if eaten incautiously. That this is true is shown by the following anecdote taken from Robert Beverly's *History and Present State of Virginia*, in his account "Of the Wild Fruits of the Country." It appears that the soldiers sent to Jamestown to quell the uprising known as Bacon's Rebellion (1676) gathered young plant of this species cooked it as a potherb.

The James-Town Weed (which resembles the Thorny Apple of Peru, and I take to be the Plant so call'd) is supposed to be one of the greatest Coolers in the World. This is being an early Plant, was gather'd very young for a boil'd salad, by some of the Soldiers sent thither, to pacifie the Troubles of Bacon; and some of them eat plentifully of It, the effect of which was a very pleasant Comedy; for they turn'd natural Fools upon It for several Days: One would blow up a Feather In the Air; another woul'd dart Straws at It with much Fury; and another stark naked was sitting up In the Corner, like monkey, grinning and making Mows at them; a Fourth would fondly kiss and paw his Companions, and swear in their Faces, with a Countenance more antick, than any In a Dutch Droll. In this frantick Condition they were confined, lest they should In their Folly destroy themselves; though It was observed, that all their Actions were full of Innocence and good Nature. Indeed, they were not very cleanly; for they would have wallow'd in their own Excrements, It they had not been prevented. A Thousand such simple Tricks they play'd, and after Eleven Days, return'd themselves again, not remembring a thing that had pass'd (7).



TREE DATURA (*BRUGMANSIA SANGUINEA*), USED AS A NARCOTIC BY THE PRIESTS OF THE TEMPLE OF THE SUN.

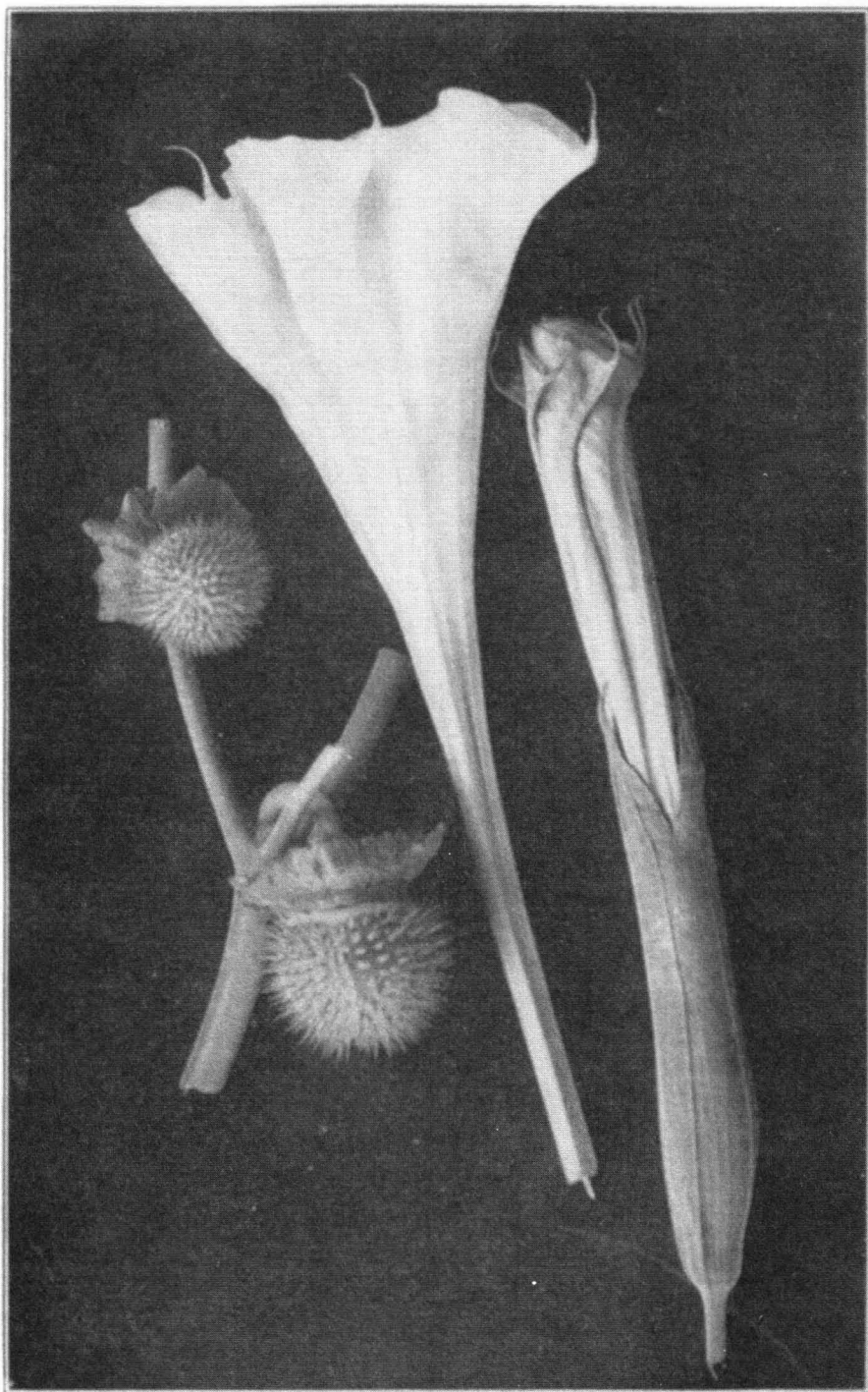
The Huaca-Cachu of Peru

The narcotic effects of *Datura sanguinea*, known in Peru as Huacacachu or Yerba de Huaca, have been described by several travelers. Tschudi, who found it growing on the declivities of the Andes above the village of Matucanas, repeats the statement of Humboldt that from its fruit the Indians prepare a very powerful intoxicant which they call tonga, on which account the Spaniards named the plant *borrachero*. His account is as follows:

The Indians believe that by drinking the tonga they are brought into communication with the spirits of their forefathers. I once had an opportunity of observing an Indian under the influence of this drink. Shortly after having swallowed the beverage he fell into a heavy stupor; he sat with his eyes vacantly fixed on the ground, his mouth convulsively closed, and his nostrils dilated. In the course of about a quarter of an hour his eyes began to roll, foam issued from his half-opened lips, and his whole body was agitated by frightful convulsions. These violent symptoms having subsided, a profound sleep of several hours succeeded. In the evening I again saw this Indian. He was relating to a circle of attentive listeners the particulars of his vision, during which he alleged he had held communication with the spirits of his forefathers. He appeared very weak and exhausted.

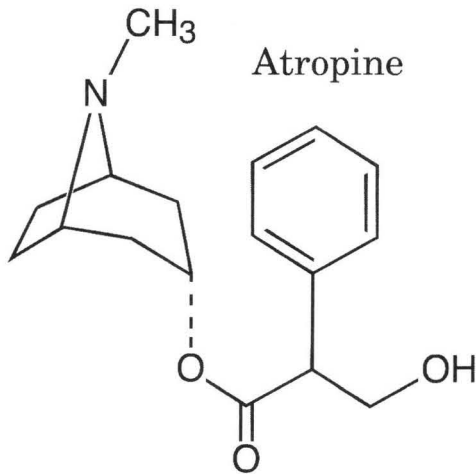
In former times the Indian sorcerers, when they pretended to transport themselves into the presence of their deities, drank the juice of the thorn apple in order to work themselves into a state of ecstasy. Though the establishment of Christianity has weaned the Indians from their idolatry, yet it had not shed their old superstitions. They still believe that they can hold communication with the spirits of their ancestors, and that they can obtain from them a clue to the treasures concealed in the huacas, or graves; hence the Indian name of the thorn-apple—*huacacachu*, or grave plant.

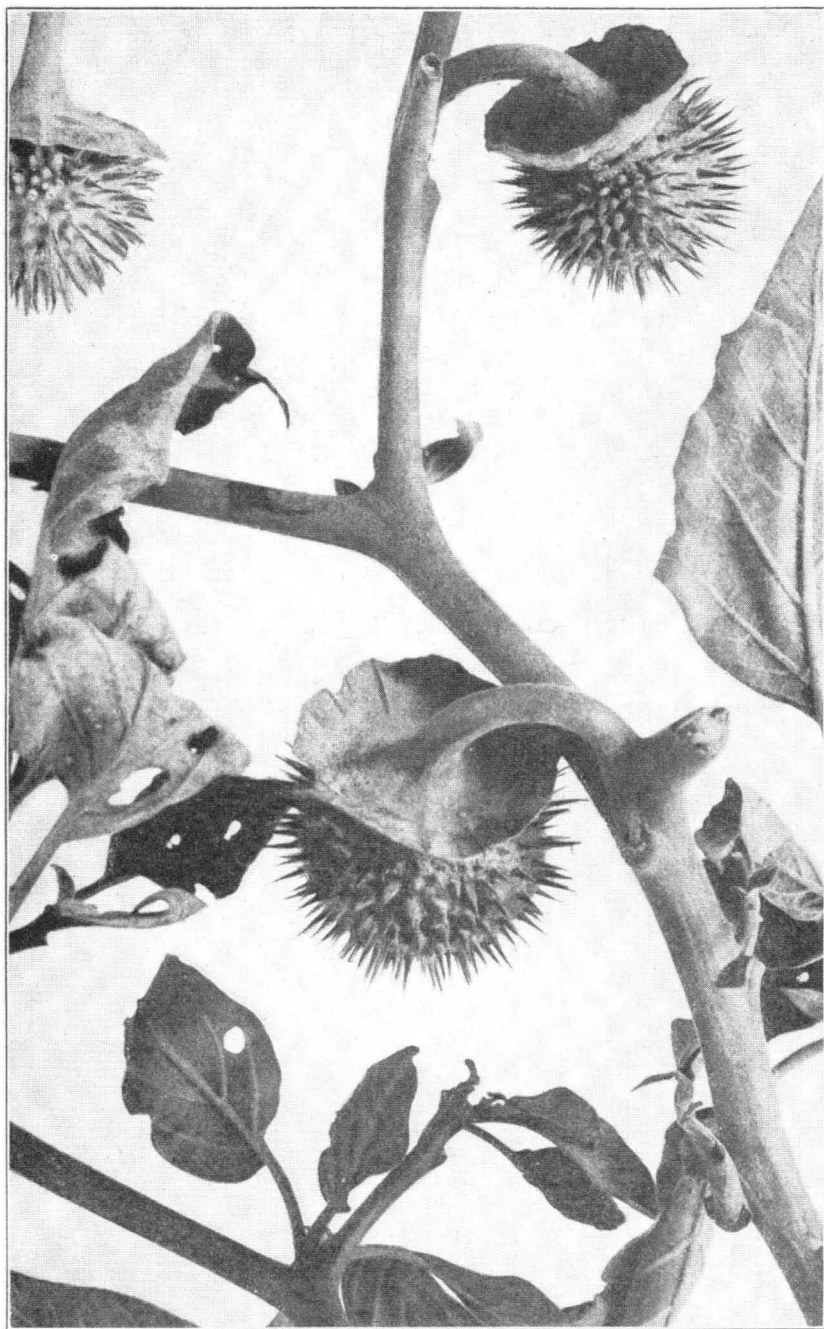
Humboldt and Bonpland, who collected *Datura sanguinea* on the banks of the Rio Mayo, in New Granada, state that the natives believe that the tonga prepared from this species to be more efficacious as a narcotic than that made from the white-flowered *Datura arborea* mentioned above. It is from the account of these travelers that the story of the Peruvian prophets is taken. The Temple of the Sun in which they officiated was at Sagamoza, in the interior of what is now Colombia. Dr. Santiago Cortés, in his account of the medicinal plants of the province of Cauca, Colombia, says that there are many stories and fables relating to this plant told by the natives.



DATURA METELOIDES, A CEREMONIAL NARCOTIC OF THE ANCIENT MEXICANS, ZUÑIS, AND CALIFORNIA INDIANS. TWO-THIRDS NATURAL SIZE.

- (1) See *Mem. de l'Acad. Roy. des Sciences*, Année 1745, p.430. 1749
 - 2) **Zoe**, 3:360. 1892.
 - 3) See *Contr. North Amer. Ethn.* 3:380 and 428. 1877.
 - 4) *Amer. Nat.* 12:650. 1878.
 - 5) See **Bourke, John G.** *On the Border with Crook*, p. 165. 1892.
 - 6) Its active principle, daturine, has been identified with the alkaloid atropine, for which it is a perfect substitute. In 1916 one firm in the United States used one and a half million pounds of this plant for the manufacture of atropine.
 - 7) [**Beverly, Robert.**] *History and Present State of Virginia*. Bk. 2, p.24. 1705.
- Source: Stafford 1916



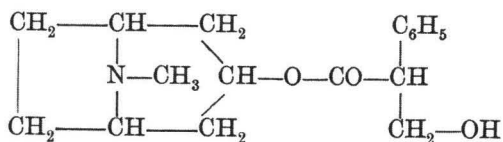


DATURA METELOIDES, NARCOTIC PLANT USED BY THE ANCIENT AZTECS, ZUÑIS, AND CALIFORNIA INDIANS AS AN INTOXICANT AND HYPNOTIC. NATURAL SIZE.

Chapter 6: Datura Alkaloids

Hyoscyamine and Atropine

$C_{17}H_{23}O_3N$ M.W. 289



by M. Barrowcliff, M.B.E., F.I.C. and
Francis H. Carr, C.B.E., F.I.C.

Atropine is the optically inactive mixture of dextro- and laevo-hyoscyamine. Laevo-hyoscyamine alone occurs in nature. The best source of hyoscyamine is a variety of henbane indigenous in Egypt, Soudan and India, known as *Hyoscyamus muticus*, in the various parts of which it has been shown to be present in the following proportions: leaves 1.4%; stems 0.6 %; seeds 0.87-1.34%. Atropine is also manufactured from the root of *Scopolia carniolica*, in which hyoscyamine is present to the extent of 0.43-0.51%; and from *Atropa belladonna*, the leaves of which contain, on the average, 0.4%, and the roots 0.5%, of hyoscyamine. Many other solanaceous plants of the Datura species contain these alkaloids, in varying, and smaller, amounts, often associated with hyoscine or scopolamine.

The drug should be dried immediately after collection and should be extracted as soon as possible, as the alkaloid content gradually diminishes on keeping.

For the manufacture of atropine and hyoscyamine the drug is powdered and extracted, in a copper extractor, by percolation with hot alcohol (S.V.M.), until free from alkaloid. The alcohol is removed from the extract by distillation, preferably under somewhat diminished pressure, and the syrupy extract is allowed to flow, in a thin stream, and with good stirring, into very dilute (0.5-1.0%) acid, hydrochloric or sulphuric. The aqueous portion is separated from undissolved resinous matter, etc., and is further freed from impurity by being shaken out with petrol. It is then made neutral, or faintly alkaline, by addition of ammonia solution, and set aside for a time, when a quantity of resinous material is precipitated and removed. An excess of ammonia is then added, whereby the alkaloids are precipitated. They are extracted by

shaking out with chloroform, and are finally freed from resinous and other impurity by being dissolved out of the chloroform extract with dilute acid, reprecipitated with ammonia, and again extracted into chloroform. The solvent is removed by distillation; and the treatment of the mixed alkaloids, consisting mainly of *l*-hyoscyamine, with a little atropine, and possibly hyoscyne, varies as hyoscyamine or atropine is required.

The alkaloid is converted by neutralisation with the required quantity of oxalic acid into the oxalate $(B)2H_2C_2O_4$ (see *Trans. Chem. Soc.* (1912), 101, 946).

This is recrystallised from water until it has the melting point of pure *l*-hyoscyamine oxalate (176°). The base is then obtained by dissolving the oxalate in water, making alkaline with ammonia and extracting with chloroform. After removing the solvent, the neutral sulphate is prepared and crystallised from alcohol or moist acetone.

Atropine Sulphate

$(C_{17}H_{23}O_3N)_2 H_2SO_4$ M.W. 676

The crude alkaloid, together with that regenerated from the mother liquors after the removal of *l*-hyoscyamine oxalate, is racemised by dissolving 52 parts in 520 volumes of 95% alcohol containing 4.16 parts of sodium hydroxide 71 (*loc. cit.*). The solution is allowed to stand, at room temperature, until it shows no optical activity, after which it is neutralised with oxalic acid, the alcohol is removed, and the oxalate recrystallised from water until a melting point of 196° - 197° is obtained. From this the base is regenerated and converted into the sulphate, as described above in the case of hyoscyamine.

Atropine sulphate is a white crystalline powder. M.p. 194° . It dissolves in 0.4 part of water, and in 4 parts of 90% alcohol. The aqueous solution is neutral in reaction, and should be optically inactive.

No colour should be imparted by the salt to sulphuric acid.

Three cubic centimetres of a 1 in 60 solution should yield no precipitate when mixed with 1 c.c. of ammonia solution (10 %)

Atropine $C_{17}H_{23}O_3N$, 289, is prepared by regenerating the base from the pure oxalate and crystallising from aqueous alcohol.

Atropine crystallises in colourless acicular crystals M.p. 115.5° . It dissolves in 450 parts of water at 25° and in 87 parts at 80° ; in 3 parts of 90% alcohol and in 1 part of chloroform. It should be optically inactive and no colour should be developed on treatment with sulphuric acid.

Hyoscyne or Scopolamine

$C_{17}H_{21}O_4N$ M.W. 303

Naturally occurring hyoscyne is a combination of laevo-tropic acid with inactive hyoscyne. It is found, mostly in conjunction with hyoscyamine, in many species of *Datura*. In *D. arborea*, *D. fastuosa*, and *D. metel*, the alkaloid consists chiefly of hyoscyne; whilst *D. stramonium* contains principally hyoscyamine, with some hyoscyne. It is present also in *Scopolia* and *Hyoscyamus* species, for instance in *Scopolia japonica* and *Hyoscyamus niger*.

Datura metel is probably the most readily available source of hyoscyne. The powdered drug is extracted with hot alcohol and the crude alkaloids are isolated in the same way as has been described under hyoscyamine, except that sodium bicarbonate is employed, instead of ammonia, for liberating the bases. The alkaloid is neutralised exactly with hydrobromic acid and the solution of the hydrobromide concentrated. The salt which crystallises out on cooling is separated and purified by recrystallisation from water, until of constant melting point.

Source: Barrowcliff 1920

Extraction of Atropine

In 1809, Vaquelin discovered atropine. Brandes recognized atropine as an alkaloid in 1819. Atropine only occurs in trace amounts in plants, but is readily obtained from the racemization of levorotatory hyoscyamine which is abundant in nightshade family. Common sources are belladonna root, Jimson Weed, *Hyoscyamus niger* and *H. muticus*.

The plant material is powdered and an aqueous solution of sodium carbonate is added to thoroughly moisten.

Ethyl ether or ethyl acetate are percolated through the mixture. Acetic acid is used to extract the bases from the solvent. The acetic acid/base solution is washed with ether until the ether absorbs no more color. The bases are precipitated with sodium carbonate, washed, dried and dissolved in ethyl ether.

The ethyl ether solution of bases is dehydrated with anhydrous sodium sulfate, filtered and the ether concentrated and cooled to crystallize a mixture of hyoscyamine and atropine. The mixture is mixed with one quarter its weight in chloroform and refluxed at 116° to 120° for 2 hours. The racemization of hyoscyamine produces atropine.

Another way to carry out the racemization is to mix the mixture of bases with sodium hydroxide and follow the reaction by optical measurement.

The crude atropine can be decolorized by the use of decolorizing carbon in acetone and filtered. The acetone is concentrated and seeded with a crystal of atropine to initiate crystallization.

Kraut demonstrated, in 1864, that atropine undergoes hydrolysis, on heating either with barium hydroxide solution or hydrochloric acid. The product is a mixture of tropine and tropic acid.

References: Cook 1936; Osol 1947



Datura stramonium

Chapter 7: Growing Datura and Related Species

BELLADONNA *Atropa belladonna*

“Belladonna Root is the dried root of *Atropa belladonna* Linné (Fam. *Solanaceae*). Belladonna Root yields not less than 0.45 percent of the total alkaloids of Belladonna Root, and contains not more than 10 per cent. of its stem bases and weedy crowns, and not more than 2 percent of other foreign organic matter, and yields not more than 4 per cent. of acid-insoluble ash.” U.S. “Belladonna Root is the root of *Atropa belladonna*, Linn., collected in autumn and dried.” Br.

Racine de Belladone, Belladone, *Fr.*; Gemeine Tollkirsche, Woldfskirschen-Wurzel. *G.*; Radice di Belladonna, *It.*; Raiz de Belladona, Belladama, *Sp.*

The belladonna, or deadly night-shade (*Atropa belladonna*) is a herbaceous perennial, with a fleshy, creeping root, from which rise several erect, round, purplish, branching stems, to the height of about three feet. The leaves, which are attached by short footstalks to the stem, are in pairs of unequal size, oval, pointed, entire, of a dusty green on their upper surface, and paler beneath. The flowers are large, bell-shaped, pendant, of a brownish-purple color, with solitary peduncles, rising from the axils of the leaves. The fruit is a roundish berry with longitudinal furrow on each side, at first green, afterwards red, ultimately deep purple and containing, in two loculi, numerous seeds and a sweetish violet-colored juice. The calyx adheres to the base of the fruit.

The plant is a native of Central and Southern Europe, where it grows in shady places, along walls, and amidst rubbish, flowering in June and July, and ripening its fruit in September. It grows vigorously under cultivation in England, France and the United States. During the past few years there has been very great interest in the cultivation of belladonna in the United States. The results of all experiments show that a high grade of belladonna can be grown in this country. (Consult Borneman, *A.J.P.*, 1909, p.1; Miller, *A.J.P.*, 1913, p.291; Carr, *Ibid*, 1913, p. 487; Sievers, *A.J.P.*, 1914, p. 483, also 1917, lxxxix, 203; Newcomb, *A.J.P.*, 1915, p.1; Kock, *J.A.Ph.A.*, 1919, p.390.) Plants cultivated in California are very rich in active constituents. The yield per acre of stems and leaves is somewhat less than one ton. The experiments in California seemed to show that the alkaloidal contents of belladonna stems is

equal to that of the leaves, ranging from 0.51 to 0.82 percent of total alkaloids. (*Pacific Pharmacist*, 1909; 1910, p. 295.) Belladonna leaves grown in the shade are uniformly larger, though somewhat thinner. It is quite likely that the percentage of alkaloids can be increased through selection (*A.J.P.*, 1914, p. 483, and 1917, lxxxix, 254.) All parts of it are active. The leaves and roots are directed by the United States and British Pharmacopoeias, the latter including the branches, which, if young, are probably not less efficient. The leaves should be collected in June or July, when the plant is in flower, the roots in the autumn or early in the spring, and from plants three to four years old. Leaves which have been kept long should not be used, as they undergo change through absorption of atmospheric moisture, emitting ammonia and probably losing a portion of their active nitrogenous matter. Seivers (*A.J.P.* 1916, lxxxviii, 193) has found that no relation exists between the appearance of the leaves and the percentage of alkaloid. He found the amount of alkaloid in leaves of cultivated plants varied from 0.30 to 0.76 percent. Specimens which contain much stem or are musty should always be rejected, as weak in active principle. Holmes has found in the English market the root of *Medicago sativa* used as an adulterant. (*P.J.*, 1882)

Both herb and root drugs are obtained for the most part from plants cultivated in the United States, Central Europe and England.

Constituents.—Belladonna contains volatile bases both of an alkaloidal and a non-alkaloidal type. They are pyridines, pyrrols and diamines. It is generally recognized that the following mydriatic alkaloids are found in the solanaceous plants; atropine, hyoscyamine, scopolamine, apoatropine, tropacocaine, meteloidine and belladonine. The first two of these, atropine and hyoscyamine, are isomeric, having the formula $C_{17}H_{23}O_3N$, and yield the same decomposition products. They differ, however, in their physical constants, especially in their relation to polarized light; whereas hyoscyamine is strongly laevo-rotatory, atropine is optically inert. Will (*B. Chem. G.*, 1888, p.1717) has shown that hyoscyamine is readily changed into atropine and that varying proportions of the two alkaloids may be obtained from the same specimen of belladonna, according to the method of extracting from the crude drug. His conclusions have been confirmed by Gorio and Coty (*Bull. d. Sciences Pharmacol.*, 1921, xxviii, 545). The studies of the latter as well as those of Schutte (*A. Pharm.*, 1891, ccxxix, No. 7) demonstrate that atropine, if it occur at all in belladonna, is in much smaller amount than hyoscyamine. Atropine appears to be a mixture of laevo-rotatory and dextro-rotatory hyoscyamines. The dextro-hyoscyamine does not appear to occur in nature, but has been prepared artificially. Of these,

atropine occurs in the *Atropa belladonna* and in *Datura stramonium*, hyoscyamine in these plants and also in *Hyoscyamus niger*, *Hyoscyamus muticus* and *Duboisia myoporoides*; scopolamine is found in *Hyoscyamus niger* and in *Scopola carniolica*, and belladonnine in belladonna root alone. Source: Wood 1926

Atropa belladonna Belladonna Cultivation

by W.W. Stockburger

Belladonna or deadly nightshade (*Atropa belladonna*) is a large, poisonous perennial which occurs wild in Europe, where it is also cultivated. Both the leaves and the roots are important crude drugs. In recent years it has been cultivated to some extent in this country, but it is likely to winterkill in the colder sections.

Belladonna may be propagated in a small way from cuttings of the young shoots rooted in moist sand in the usual manner or from divisions of the fleshy rootstocks made early in the spring, but it is most readily grown from seeds which may be thinly sown in pots or well-drained boxes in a cool greenhouse in midwinter or in a sheltered place in a garden early in the spring. When the seedlings are large enough to handle they should be transplanted singly to small pots or pricked out in flats or shallow boxes of light, rich soil, placing them about 2 inches apart each way, as with tomato or other vegetable plants intended for field planting. In the spring, as soon as danger from frost is over, they should be transplanted to the field and set about 20 inches apart in rows 30 or more inches apart. Sowing seeds in the field or transplanting directly, from the seed bed to the field has rarely given good results in this country. Belladonna seeds are small, and if well handled under glass or in protected seed beds 1 ounce should produce 10,000 or more plants, sufficient to set an acre.

Belladonna thrives best in deep, moist, well-drained loam containing lime, such as will under proper fertilization produce good garden vegetables. The preparation of the soil should be very thorough, and consists of deep plowing, in either fall or early spring, and repeated working with the disk or springtooth and smoothing harrows. Weeds should be kept under control at all times and the soil stirred with a hoe or cultivator at intervals of about 10 days, particularly after each hard rain, and shallow cultivation given in hot, dry weather to conserve the natural moisture of the soil. Good commercial fertilizers, such as are

commonly used in truck gardens, are beneficial. Those containing 8 per cent of phosphoric acid, 4 per cent of nitrogen, and 4 per cent of potash are the most desirable, and should be applied at the rate of about 600 pounds per acre. Stable manure at the rate of 12 to 20 tons to the acre may be used if plowed under when the ground is prepared.

Belladonna is sometimes affected by a wilt disease, which is aggravated by wet soils and fresh animal manures, and the foliage is greedily attacked by the potato beetle. Dusting with lime, soot, or road dust in the morning when the leaves are wet with dew is occasionally effective. The destructive attacks of these pests are usually confined to the seed bed or to first-year plantings, but the insects may be controlled by the careful use of insecticides.

The leaves are picked when the plants are in full bloom. They should be carefully handled, to avoid bruising, and dried in the shade in order to retain their green color. A hundred pounds of fresh leaves yield about 18 pounds when well dried. One crop only can be collected the year of planting, but two crops are gathered in each of the next two or three years, after which it appears better to market the roots and make new plantings. While only the leaves should be collected for the best pharmaceutical trade, the young growth, including the smaller sappy twigs, has medicinal value and may be sheared from the plants and dried in the same manner as the leaves. The ease of collection and the increased weight of material may render the latter method more profitable.

The roots alone are not as profitable as the leaves. The best roots are those of the second and third year's growth. They are harvested in the fall after frost, the tops being mowed and raked off and the roots turned out with a deep-running plow, or with a potato fork if the area be small. They are carefully washed and cut into about 4-inch lengths, the larger pieces being split lengthwise to aid in drying. Thorough drying either in the sun or with mild artificial heat is essential; otherwise the roots will mold when stored.

The high prices paid for belladonna during the war greatly stimulated the cultivation of this crop, which had previously been grown with some success in California, Michigan, Indiana, Pennsylvania, New Jersey, and some other States. In 1918, 273 acres of belladonna were harvested, the total production being about 83 tons of herb (including leaves and stems), an average of 600 pounds per acre. From 136 acres 11 tons of root were harvested, an average of 164 pounds per acre. Quotations in July, 1935, were 14 to 15 cents a pound for the leaves and 13 to 14 cents a pound for the root. Source: Stockburger 1935

Datura stramonium L. (Jimson Weed)

by V.K. Chesnut

Other names: Jamestown weed; common stramonium; thorn apple, apple of Peru; devil's apple; mad apple; stinkwort; stinkweed (W.Va.); Jamestown lily (N.C.); white man's plant (by Indians).

Description and where found.—

The jimson weeds are rank ill-smelling plants with large funnel-shaped flowers and prickly four-valved seed pods. They are mostly weeds which have been introduced into the United States from Europe and tropical America. The present species is a stout, smooth, bushy annual 2 to 5 feet high, with a coarse green stem, large flaccid leaves, and white, heavy-scented flowers 2 to 4 inches long. The flowers appear from May to September, and the fruit ripens from August to November, according to latitude. The seeds are numerous and about the size of a grain of buckwheat. When fresh, they are ill-scented and nauseating, but later they are not so disagreeable. The nectar is sweet, but a little nauseating. The jimson weed is native to Europe and Asia, but is now commonly introduced in waste grounds about dwellings in all of the States east of Iowa and Louisiana with, perhaps, the exception of Minnesota. It is common in eastern Kansas and Nebraska, and in some parts of Colorado, and has probably obtained some foothold in all of the Western States.

The purple-stemmed jimson weed (*Datura tatula*) is a somewhat taller plant, with purplish flowers and stems, but otherwise practically identical with the preceding, both in botanical and toxic characters. It is more abundant toward the South and West than the other.

Ways of poisoning.—Cases of poisoning arise in adults from excessive use as a stimulant or as a medicine. Children are sometimes tempted to eat the fruit if they are permitted to play where the weed is to be found. Several cases of this kind were reported to this Department during the fall of 1897. At Alpena, Mich., five children were badly poisoned in August by eating the seeds of the purple-flowered species, which was cultivated in a garden as a curiosity under the fanciful trade name of "Night-blooming Cactus." Several other cases where children have been poisoned by this plant have been reported. Children are also poisoned by sucking the flower or playing with it in the mouth. The fresh green leaves and also the root have occasionally been cooked by mistake for other wild edible plants. One or two instances are recorded in which cattle have been poisoned by eating the leaves of young plants which were present in grass hay.

Symptoms.—The symptoms of the poisoning are headache, vertigo, nausea, extreme thirst, dry, burning skin, and general nervous confusion, with dilated pupils, loss of sight and of voluntary motion, and sometimes mania, convulsions, and death.

The jimson weeds should be removed from vacant lots by mowing the plants while in flower or by cultivating the soil.

Source: Chesnut 1898

Datura stramonium Jimson Weed Cultivation

by W.W. Stockburger

Stramonium, Jamestown weed, or jimson weed (*Datura stramonium*), is a poisonous annual of the nightshade family, which occurs as a common weed in almost all parts of this country except the West and the North. The leaves and seeds are used medicinally.

Although stramonium grows wild on a variety of soils, it thrives best under cultivation in rich and rather heavy soils which are fairly well supplied with lime. It grows readily from seed, which may be sown in the open early in the spring in drills 3 feet apart and barely covered. When the plants are well established they are thinned to stand 12 to 15 inches apart in the row. The plants can be readily transplanted, and gaps occurring in the rows may be filled in with the plants removed in thinning. Cultivation sufficient to keep the soil free from weeds is necessary for good growth.

Cultivated plants are frequently attacked by leaf-eating insects, especially in the early stages of growth, and it is often necessary to use lime or other insect repellents to prevent the destruction of the crop.

The leaves, which are collected when the plant is in full bloom, may be picked in the field, but time will be saved if the entire plant is cut and dried in an artificially heated curing room at a temperature of 100° to 110° F. When the leaves are dry they can be readily stripped from the stems, and should be baled for shipment. Such seed as is ripe may be easily threshed out of the capsules after the leaves have been removed from the stems.

Yields of dry leaf at the rate of 1,000 to 1,500 pounds per acre have been obtained. The yield of seed is much more variable, and is estimated to range from 500 to 2,000 pounds per acre. The price in July, 1935, for the leaves was 10 to 11 cents and for the seed 9 to 10 cents a pound. Source Stockburger 1935

Hyoscyamus niger Henbane Cultivation

by W.W. Stockburger

Henbane (*Hyoscyamus niger*) is a poisonous annual or biennial herb of the nightshade family, introduced into this country from Europe and occasionally found as a weed in a number of the Northern States. The leaves, flowering tops, and sometimes the seeds are used medicinally.

Henbane is propagated from seeds, but when these are sown in the open field germination is uncertain, and a very poor stand or total failure is a frequent result. Germination is usually much more certain when the seeds are sown under glass, but the plants do not readily stand transplanting and often die after they are set in the open. Very good results have been obtained by sowing the seed in small pots under glass in January, transferring the seedlings to 3-inch pots in March, and transplanting in May to the field, where the plants may be set at least 15 inches apart in rows. In handling the plants care should be taken to disturb the soil about the roots as little as possible. The soil requirements and method of cultivation are practically the same as for belladonna.

The leaves of henbane usually suffer severely from attacks of the potato beetle, especially during the first year, and the crop is very likely to be destroyed if grown within the range of this insect.

Ordinarily the plants blossom about August of the second year and die after ripening their seed, but individual plants started early frequently bloom and set seed the first year. The leaves and flowering tops are collected when the plants are in full bloom and are carefully dried in the shade.

The American crop of henbane has never much exceeded 10 acres. The yield under favorable conditions is estimated at about 600 pounds per acre. The wholesale price in July, 1935, was 28 to 24 cents a pound. Source Stockburger 1935

Solanum nigrum L. (Black Nightshade)

by V.K. Chesnut

Other names: Common nightshade; nightshade; deadly nightshade; garden nightshade.

Description and where found.—The black nightshade is a smooth annual, 1 to 2 feet high, with rough, angular, widely branching stems;

ovate leaves, 2 to 4 inches long, with wavy margins; drooping clusters of small white flowers, and black, globose, juicy berries, which ripen from July to October. It is a common introduced weed in rich shaded grounds and fields east of South Dakota and Arkansas, and in damp places westward to the Pacific Ocean.

Poisonous properties.—The amount of poison present in any part of this plant varies with the conditions of growth. The more musky-odored plants are the most poisonous. In some, the amount of alkaloid in the ripe fruit and leaves is so small that these parts may be, and are, consumed in considerable quantity without any ill consequences. Poisoning does sometimes follow, but it is not clear whether this is due to improper preparation or to careless selection of the parts used. The use of black nightshade for food is certainly not to be recommended. Cases of poisoning are recorded for calves, sheep, goats, and swine.

Symptoms.—The characteristic symptoms are about the same in man and animals. They are stupefaction, staggering, loss of speech, feeling and consciousness; cramps, and sometimes convulsions. The pupil of the eye is generally dilated. Death is directly due to a paralysis of the lungs, but fortunately few cases are fatal.

Nearly related to this plant is the spreading nightshade or "wild potato" (*Solanum triflorum* Nutt.), a native garden weed of the Great Plains region. It is a smooth, low annual, with widely branching stems, 7 to 9 lobed leaves, numerous clusters of small white flowers which are grouped in threes, and large green berries a half inch or more in diameter. These are not attractive to the eye, but have an agreeable odor and taste.

Complaints of the poisoning of cattle by this plant have been sent in to the Department from Nebraska, and experiments show that the berries are poisonous. No cases of human poisoning have been reported.

The plants of either of these species may easily be killed by cutting them down before the fruit matures.

Source: Chesnut 1898



Solanum nigrum

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